FUNCTIONAL AND DIFFUSION MRI BIOMARKERS OF MILD COGNITIVE IMPAIRMENT

by

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(Under the Direction of L. Stephen Miller)

ABSTRACT

Mild cognitive impairment (MCI) is often viewed as an intermediate phase between normal aging and Alzheimer's disease (AD). Consequently, it is important to identify biomarkers of this pre-clinical phase of AD in order to provide preventative treatments. In the present study, MCI participants underwent functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) scanning. FMRI data was acquired while participants performed a complex working memory span (CWKMS) task and DTI diffusivity indices were correlated with performance on cognitive measures. FMRI findings suggest that superior temporal gyrus hyper-activation during CWKMS performance may be a previously undiscovered biomarker of memory impairment in MCI. Performance on a delayed memory measure demonstrated widespread negative correlations with DTI diffusivity measures in those with MCI along several pathways connecting cortical regions involved in memory performance, suggesting that impaired memory performance in MCI and AD may be compounded by global white matter deterioration. Altogether, functional and structural imaging biomarkers of MCI were

identified which may further aid in elucidating the causes of memory impairment in MCI and providing targeted treatments.

INDEX WORDS: Mild cognitive impairment, dementia, working memory, white matter, functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI)

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

The detection of abnormal cognitive decline in older adults is of significant importance, especially as older adults increasingly constitute a greater portion of the population. The most recent statistics (2009) on older individuals indicate that there are 39.6 million individuals over the age of 65 residing in the United States, approximately 13% of the population. By 2030 that number is expected to increase to 72.1 million, or 19% of the population (Vincent & Velkof, 2010). In 2000, it was estimated there were approximately 606 million individuals over the age of 60 across the world; by 2050, that figure is projected to reach 2 billion. A major concern often associated with aging and cognitive decline is the onset of dementia, most commonly occurring as Alzheimer's disease (AD). Prior to the onset of a diagnosable dementia is a period of gradual, but possibly fluctuating, increase in cognitive impairment, termed mild cognitive impairment (MCI). As the term suggests, impairment during MCI is not severe, but can affect more than one cognitive domain.

Several biomarkers associated with developing AD are also associated with the development of MCI, often seen as the precursor to AD. Recent guidelines developed by a joint National Institute on Aging and Alzheimer's Association workgroup (Albert et al., 2011) indicate that some of the most reliable biomarkers of AD pathology are those indicative of beta amyloid-42 ($A\beta_{42}$) and tau deposition. It is suggested the aggregation of these two proteins often results in neuronal injury, often evidenced as medial temporal

atrophy, and hypometabolism or hypoperfusion in temporoparietal cortex or the precuneus. The workgroup also indicated that the presence of the apolipoprotein E ε4 (APOE ε4) allele is the only genetic factor widely accepted as indicative of an increased risk of developing AD.

Here, the aim is to use magnetic resonance imaging (MRI) to further increase the repertoire of available biomarkers useful in the diagnosis of MCI. The first imaging biomarker of interest is the functional MRI (fMRI) detected hemodynamic response in regions of interest (ROIs) associated with working memory (WKM) performance. WKM is a high level cognitive mechanism that integrates short-term memory (STM) and long-term memory (LTM) functioning through the use of several executive control functions, mainly attentional control. Since WKM is a multi-domain cognitive mechanism, evaluating WKM deficits in patients with MCI may capture impairments across a variety of domains. As such, evaluation of WKM performance across MCI subtypes may provide another marker by which to predict conversion to AD. WKM ROIs include the dorsolateral and ventrolateral prefrontal cortices (DLPFC, VLPFC), anterior cingulate cortex (ACC), superior parietal lobule (SPL), inferior parietal lobule (IPL), precuneus, and the medial temporal lobes (MTL).

The second set of imaging biomarkers of interest are diffusivity indices of water surrounding the white matter gained from diffusion tensor imaging (DTI). These indices are believed to reflect several features indicative of white matter integrity and can therefore be used to infer microstructural changes. For example, axial diffusivity (DA) indicates the extent of water diffusivity parallel to the axon. Changes in DA are seen as an indicator of the extra- or intra-axonal changes that occur along with

neurodegeneration. Other commonly used indices are radial diffusivity (RD; diffusion perpendicular to DA), mean diffusivity (MD; average diffusion of water within the voxel of interest), fractional anisotropy (FA; the degree to which water diffuses along DA). A meta-analysis by Sexton et al. (2011) indicated a large effect size for increased MD in the hippocampus and parietal lobes and reduced FA in the hippocampus in those with MCI. Furthermore, MCI patients with predominantly impaired executive functions have been shown to exhibit increased DR and MD in the white matter of frontal, cingulate, and entorhinal cortices relative to controls (Grambaite et al., 2011). To further explore the meaning of these white matter changes it would be beneficial to investigate their correlation with scores on neuropsychological batteries, such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), a battery often used in the assessing the progression of dementia.

Normal Cognitive Aging

A normal part of the aging process is an often small, but steady decline in specific cognitive abilities. Normal cognitive aging typically begins to manifest during early adulthood and is evidenced as the decline of general fluid abilities, such as those of memory, problem solving, spatial abilities, and processing speed (Christensen et al., 2001). Even though these cognitive processes influence and depend on each other, it appears that a decrease in processing speed shows one of the strongest correlations with age (Salthouse, 2000). Park et al. (2002) demonstrated that short-term, working, and long-term memories continuously decline throughout the adult life-span (beginning at approximately 20 years of age) at a steady rate, with processing speed being the most influential factor mediating the variance between cognitive tasks and age. Implicit

memories, though, are less susceptible to age-related decline (Luo & Craik, 2008). Specifically, crystallized abilities, such as those of vocabulary and general knowledge, continue to be acquired until the sixth or seventh decade of life (Christensen et al., 2001; Park et al., 2002).

Salthouse (1996) proposed two mechanisms responsible for the relation between cognitive ability and processing speed, the limited time and simultaneity mechanisms. The limited-time mechanism suggests that the reduction in speed at which an operation is completed impairs the quality of processing of proceeding operations. In other words, given a limited time frame in which a series of operations should optimally be performed, the prolonged processing of early operations restricts the amount of time available for later operations. This is especially important when there are demands for concurrent processing. Similarly, the simultaneity mechanism suggests that reduced processing speed impairs an individual's ability to manage or synchronize several cognitive operations or pieces of information needed for higher level processes. The inability to efficiently synchronize information to be fed into higher level processes within a limited temporal window becomes problematic because information may decay or be displaced over time. Therefore, the cognitive slowing associated with normal aging may be explained as a result of reduced processing speed (Salthouse, 1985; Salthouse 2000).

Neurologically, the normal decline in cognitive abilities may occur for a variety of reasons, the most global likely being age related brain atrophy. Previously, it was thought that atrophy occurred due to neuronal loss, but the current literature suggests it may be due to neuronal shrinkage and loss of inter-neuronal connections (Akiyama et al., 1997; Raz, 2005), resulting in reduced or inefficient intra- and inter-regional

communication. In a neuroimaging review on brain atrophy on normally aging adults, Fox and Schott (2004) found longitudinal rates of global brain atrophy occurring at a rate of 0.2% a year at age 30-50, and increased to 0.3-0.5% at 70-80. A one year longitudinal study based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) data-set (Fjell et al., 2010), which screened for any incipient cognitive disorders, demonstrated that in a sample with an age range of 63.0 – 90.2 years of age and a mean of 76.8 years at baseline, cortical atrophy occurred at a rate 0.31% to 0.98% per year. Studies reporting regions of greatest atrophy have demonstrated some variability, partly dependent on whether the data was collected cross-sectionally or longitudinally, with longitudinal estimates showing higher rates of atrophy (Fjell et al., 2009; Raz et al., 2005). Evidence of the wide range of variability in atrophy-related findings is demonstrated in the following examples. Resnick et al. (2003) reported that gray matter atrophy is more prominent in the frontal and parietal lobes while white matter atrophy appears to be global. Raz et al. (2005) report that the largest effect sizes for change occur in the cerebellum, caudate, hippocampus, lateral PFC, and IPL. Changes in the IPL, though, were reported to lack consistency across individuals. Lastly, Fjell et al. (2010) paracellated the cortex into 33 sulci and gyri, and segmented into subcortical regions into 15 ROIs and report that the greatest atrophy in healthy older adults was found to occur in the hippocampus.

Mild Cognitive Impairment

When cognitive decline exhibits a rapid progression without incidence of an external or traumatic event it is often attributed to neurodegenerative or vascular disease. In the aging population significant declines in cognitive ability typically result from

dementing processes, of which the most common is AD. Unlike with normal aging, the primary cause of cognitive decline in AD is impaired memory functioning. Preceding the stages of readily observable and increasing deficits seen in dementia is a period of mild, but still observable clinical impairment; this period is often termed MCI. Even though varying, clinic-based estimates indicate 10-15% of those with amnestic-MCI (a-MCI) convert to AD annually (Roach, 2005), while population based estimates report conversion rates of 5-10% (DeCarli, 2003; Panza et al., 2005). Overall, of the 13.9% of individuals over the age of 70 undergoing a dementing process, AD is thought to account for approximately 69.9% of cases (Plassman et al., 2007).

Initial guidelines for AD diagnosis established in 1984 did not include a category for classification of individuals not meeting the clinical criteria for a dementia diagnosis but exhibiting MCI (McKhann et al., 1984). Since then, various attempts have been made to accurately define and categorize MCI (e.g., Crook et al., 1986; Levy, 1994; Petersen et al., 1999; Albert et al., 2011). Due to the nature of the concept of MCI, however, its diagnosis is still a questionable and complicated endeavor. One of the earliest and most well-known criteria for the diagnosis of MCI specify that a diagnosis be made if patients fulfill the following criteria: 1) subjective memory complaint, 2) objective memory impairment, 3) general cognitive functioning is not impaired, 4), no impairment in activities of daily living, and 5) not demented (Petersen et al., 1999). These criteria describe the most prominent subtype of MCI, a-MCI. Clarifications to these criteria and further subtypes were suggested by Petersen et al. (2001) and Petersen (2004).

One of the main sources of debate in the MCI diagnosis literature regards what should be considered objective memory impairment. Petersen et al. (1999) reported that

mean standard deviation on memory scores for their Mayo Clinic-based MCI cohort was 1.5 below their age-matched controls. Erroneously, this standard deviation has often been used as a cutoff score for categorizing individuals as mildly cognitively impaired; this score was not intended to be used as a cutoff, since approximately half of the MCI cohort fell below that score. Classification based on this standard deviation of memory scores becomes even more problematic when it involves individuals with initially superior abilities, primarily because premorbid measures of cognitive abilities are usually not available. In other words, even though these individuals may not exhibit differences when compared to other healthy older adults, they may be functioning significantly below their own premorbid levels, for which data is not available. As such, it is emphasized that in considering a diagnosis of MCI, clinical judgment must be used and combined with the information from the first criterion (e.g., Petersen, 2004; Petersen et al., 1999). Similar procedures should be considered when examining general cognitive functioning.

In regards to the subtypes, three other subtypes exist besides a-MCI. They are single nonmemory domain MCI, also referred to as non-amnestic MCI (na-MCI), and multiple domain MCI with or without a memory impairment md-MCI + a and md-MCI – a, respectively (Winblad et al., 2004). Those with single nonmemory domain MCI exhibit impairment in a single nonmemory domain. One of the purposes of this classification scheme is to increase the prognostic accuracy in regards to the different dementias (Petersen et al., 2001; Petersen, 2004). A-MCI is thought to be the most prognostic of AD, while md-MCI + a may also be prognostic (Petersen et al., 2004) The md-MCI subtype in general, though, is thought to be the most variable as it may indicate progression to AD, vascular dementia, or dementia with Lewy bodies. Previous research

has indicated that na-MCI is prognostic of dementia with Lewy bodies or frontotemporal dementia (Petersen & Morris, 2005; Yaffe et al., 2006).

More recent efforts at improving prognostic ability demonstrate that the profiles just described are not so straightforward. These studies indicate that those with na-MCI also demonstrate high levels of conversion to AD, while both a-MCI and na-MCI patients are also at an increased risk for conversion to non-AD dementia types (Fischer et al., 2007; Rountree et al., 2007). There is a general consensus, though, that those with MCI who convert to dementia face an increased risk of converting to AD over other dementias. It is important to note, however, a meta-analysis by Mitchell and Shiri-Feshki (2009) reported that typically less than half of those with MCI will convert to dementia.

Several studies aimed at defining the neuropsychological profiles of those with MCI have shown that those with MCI typically experience a decline in specific cognitive domains. When compared to controls on multiple domains it was shown that those with MCI exhibited deficits in episodic memory, semantic memory, and processing speed (de Jager et al., 2003). Saunders et al. (2010) demonstrated that those with a-MCI and subjective MCI displayed impairments in language retrieval, complex sustained attention, target detection, spatial WKM, and visuospatial span; those with a-MCI displayed greater deficits in selective attention, simple sustained attention, and language retrieval. Therefore, using neuropsychological measures sensitive and specific to different cognitive domains revealed that 83% of the a-MCI group demonstrated impairment in at least one other cognitive domain than episodic memory, many of which are components of WKM. Impairment in MCI, therefore, is much more inclusive of other cognitive

domains than is specified in the Petersen criteria, and the rate and patterns of memory decline are not clear (Belleville et al., 2008).

One brief neuropsychological battery which shows some promise in the diagnosis of MCI is the RBANS, as one of its primary purposes is the assessment and longitudinal testing of individuals believed to be undergoing a dementing process (Randolph, 1998). The RBANS consists of a series of subtests examining immediate memory (IM), delayed memory (DM), attention (ATT), language (LAN), and visuospatial / constructional skills (VSC). An examination of the diagnostic accuracy of the RBANS in MCI found that specificity values for all memory-related subtests and indices was 0.82 or higher, but sensitivity values were poor (Duff et al., 2010). A couple of caveats to these findings are that individuals were classified as MCI based almost entirely on their performance on other cognitive measures and only those classified as a-MCI were examined. Another study, also initially basing MCI classification on performance on other measures, found that percent retention scores on RBANS List Learning and Story Memory demonstrated excellent specificity and sensitivity in distinguishing those with MCI from normals and AD (Clark et al., 2010). Therefore, not only is there a need to further study and clarify the relationship between MCI and dementia development, as alluded to in the previous paragraph, but there is also a need to further examine whether brief neuropsychological batteries, such as the RBANS, may provide additional clinical utility in diagnosing MCI .

Current criteria for the classification of mild cognitive impairment

The latest criteria for the diagnosis of MCI have been proposed by a National Institute on Aging and Alzheimer's Association joint workgroup and provide both clinical and research criteria (Albert et al., 2011). The core clinical criteria are very

similar to previously proposed criteria and are as follows: 1) concern regarding a change in the individual's level of cognition; preferably corroborated by a collateral, 2) impairment in one or more cognitive domains, 3) preservation of independence in functional abilities, and 4) not demented. The guidelines indicate that individuals with MCI often score 1 to 1.5 standard deviations below their age, education, and demographics matched peers on one or various domains.

Since the diagnosis of MCI often revolves around determining whether an individual might progress to AD, the research criteria follow the clinical criteria while also assessing biomarkers most often associated with AD, mainly deposition of beta-amyloid (Aβ) protein (resulting in plaques) and hyperphosphorylated tau protein (resulting in neurofibrillary tangles). Typically, post-mortem examinations of individuals with probable AD look for direct evidence of $A\beta_{42}$ and tau protein deposition/aggregation in the brain for a confirmatory diagnosis. With in-vivo patients, cerebrospinal fluid (CSF) samples are examined for lower levels of $A\beta_{42}$ and increased levels of tau or hyperphosphorylated tau, while positron emission tomography can be used to detect amyloid pathology in the brain. The drawback to using only $A\beta_{42}$ or tau as a biomarker for AD related pathology is that they are not specific to AD. For example, tau is thought to be one of the causative factors of frontotemporal dementia (Small & Duff, 2008), while both $A\beta_{42}$ and tau are found in up to a third of patients who survive after a single traumatic brain injury for at least one year (Johnson et al., 2012). Evidence of both low CSF $A\beta_{42}$ and elevated CSF tau, though, are highly prognostic of conversion from MCI to AD (Albert et al., 2011).

Another important set of biomarkers included in the research criteria are those reflective of neuronal injury, one of which is elevated CSF tau levels. Other biomarkers of neuronal injury discussed in the Albert et al. (2011) criteria include: loss of hippocampal volume as seen on MRI, reduction of glucose metabolism in temporoparietal cortex, and changes in DTI and fMRI measures. All together, the presence of the core clinical criteria can be combined with biomarker information to categorize whether the MCI syndrome may be due to AD or not. The three proposed categories are 1) MCI due to AD—high likelihood, where there are positive biomarkers for both $A\beta_{42}$ and neuronal injury; 2) MCI due to AD—intermediate likelihood, where only one biomarker is tested and present; and 3) MCI—unlikely due to AD, where the presence of both biomarkers is negative. Notice that these criteria do not classify MCI individuals into the four previously discussed sub-types.

Apolipoprotein ε4: Genetic risk factor for Alzheimer's disease

The most well-known genetic risk factor for developing late-onset AD is the presence of the APOE ε4 allele. Those heterozygous for ε4 have a threefold risk of developing AD, while those who are homozygous for ε4 have a tenfold risk of developing AD. Apolipoproteins, themselves, are carrier proteins which bind with phospholipids to form lipoproteins; these lipoproteins carry the cholesterol and lipid molecules essential to cellular function. Apolipoproteins, then, are an essential part of the cellular transport mechanism. For example, in the brain the APOE receptor 2 (APOER2) binds to APOE containing lipoproteins in order to extract the lipids and cholesterol necessary for neuronal membrane remodeling and synaptic plasticity (He et al., 2007). One of the reasons why APOE allele type is so closely linked with development of AD is

that amyloid precursor protein (APP) and APOER2 are part of a cellular complex. When APOE binds to this complex, the whole complex is endocytosed along with β-secretase, a protease which cleaves APP to form Aβ. The presence of ε4 in this process has been shown to result in greater production of Aβ than ε2 or ε3, possibly because ε4 forms a stronger bond with APOER2 than ε2 or ε3 (He et al., 2007).

Since APOE ε4 is associated with Aβ it is reasonable to expect that ε4 carriers with MCI would emulate their AD counterparts to a greater extent as demonstrated by significantly greater differences in brain regions typically associated with AD, such as the medial temporal lobes, and in their functional abilities. In a voxel based morphometry study, stable MCI subjects carrying the ε4allele displayed atrophy in the amygdala and anterior hippocampus compared to those who did not carry the allele. Among subjects progressing to dementia, those with the ε4 allele showed atrophy in the left inferior frontal gyrus (IFG) and banks of the intraparietal sulcus compared to non-carriers (Hamalainen et al., 2008). He et al. (2009) found that those classified as a-MCI had greater hippocampal atrophy and were significantly more likely to be at least heterozygous for the ε4 allele. Conversely, those with na-MCI were found to have increased vascular risk factors and a lower prevalence of the APOE ε4 genotype.

In a longitudinal study, Okonkwo et al. (2010) provide further evidence of the possible detrimental effects of the APOE ε4 genotype, specifically in relation to functional abilities as measured by the Pfeffer Functional Activities Questionnaire (FAQ). In general, MCI individuals presenting with the APOE ε4 genotype demonstrated a faster rate of decline on the FAQ compared to those negative for APOE ε4. The group also examined another factor, ventricle-to-brain-ratio (VBR) and found that increased

VBR also resulted in increased rate of decline on the FAQ. When these two factors were examined jointly, it was found that the impact of VBR on FAQ score was three times greater for those positive for APOE ε4.

In general, it appears that MCI individuals who are at least heterozygous for APOE ε4 will likely experience greater brain atrophy, especially in the MTLs, and a more rapid cognitive decline than non-APOE ε4 carriers.

Working Memory

Definition

The human brain's ability to attend to various perceptual experiences, or cognitions, and to simultaneously process these pieces of information is limited (Broadbent, 1958; McElree, 2006). In order to successfully comply with task or situational demands it is often required that various pieces of information be processed in conjunction or that recently accessed or perceived information be brought back into and maintained in the focus of attention, otherwise known as STM. Maintenance of these items in the focus of attention allows them to be manipulated, associated with incoming items or with items retrieved from LTM, and/or passed into LTM. WKM allows for these complex cognitive processes to take place (Baddeley & Hitch, 1974; Cowan, 2005; Engle et al., 1999; McElree, 2006; Unsworth & Engle, 2007a). The WKM system is also crucial in maintaining information in the focus when attentional control is necessary to override automatic responses (Unsworth & Engle, 2007b). This indicates the WKM system is closely intertwined with aspects of executive functioning; specifically, the ability to maintain information in the focus of attention or exchange information between the focus and LTM is limited by the individual's level of attentional control. Furthermore, because

one of the building blocks of the WKM system is the focus of attention, a capacity limited store, WKM itself is a capacity-limited store.

One of the most well-known attempts to define the components of the WKM system has been Baddeley and Hitch's (1974) tripartite model of WKM. The Baddeley and Hitch (1974) model was novel because it did not have a single, unitary store for items in STM as was proposed in earlier models of human information processing (Atkinson & Shiffrin, 1968; Miller, 1956). Rather, it proposed separate verbal (phonological loop) and visual (visuospatial sketchpad) stores that were independent of each other and were regulated by a central executive system. Recently, the tripartite model was revised to include an episodic buffer which can integrate information from various modalities (Baddeley, 2000). Essentially, the model now has 3 separate stores for types of items in the focus of attention. Being that the episodic buffer can integrate information from the visuo-spatial sketchpad and the phonological loop, the model is effectively reverted to a unitary model of the focus of attention, similar to several current models of WKM functioning (e.g., Cowan, 1999; McElree, 2001 Unsworth & Engle, 2007b).

Recent studies concerning the WKM system have focused more on defining WKM capacity rather than defining the actual components of WKM. Cowan's (1988, 1999) embedded processes model proposes that the main differences in WKM capacity between individuals stem from their ability to keep their attention on the task at hand by suppressing interference from environmental stimuli or the activation of other LTMs caused by irrelevant cognitions (Cowan, 2001). As with the tripartite model, the embedded processes model emphasizes the role of executive functioning, especially attentional control, in regulating WKM processes. In a similar manner, Unsworth and

Engle's (2007b) active maintenance and controlled retrieval model emphasizes that WKM is required in order to override our automatic responses to a stimulus or event; one must also be able to maintain the desired outcome or response set in mind in order to override the automatic response. Therefore, this model posits that WKM capacity differences arise not only from the ability to actively maintain information in the focus of attention, but also from the ability to accurately retrieve task relevant information in the presence of irrelevant, distracting information. As can be seen, both models offer fairly similar views of the processes that affect WKM capacity. Therefore, individuals have a low WKM capacity because they have difficulty maintaining relevant information in the focus of attention in the face of task irrelevant information, regardless of whether the irrelevant information is internally generated or externally perceived (Engle & Kane, 2004). Their problems are further aggravated because they often fail to generate the proper temporal-contextual cues needed to engage in a controlled search of information residing in LTM in order to retrieve items back into the focus of attention (Unsworth & Engle; 2007b). Where these two models differ is in their slightly different views of structure of the WKM system. The embedded processes model has an intermediary level between the focus and LTM, called activated memory, in which items recently displaced from the focus reside to allow for quicker access; this intermediary construct is absent from the active maintenance and controlled retrieval model.

Working memory in healthy older adults

As previously mentioned, part of the aging process is a small, but continuous decline in general fluid abilities which begins during early adulthood. One system that exhibits a notable age-related decline is the WKM system (Bopp & Verhaeghen, 2005;

Pratt et al., 1989; Salthouse, 1992; Salthouse, 1994; Salthouse & Babcock, 1991). One hypothesis states that impairments in WKM abilities may be responsible for overall age-related cognitive decline (Mayr & Kliegl, 1993). It is also possible, though, that this age-related impairment may be restricted to tasks of executive control requiring maintenance of more than one task set, as in dual-task performance, but not for tasks of inhibition or selective attention, such as the Stroop task (Verhaeghen & Cerella, 2002).

In a meta-analysis of the aging and verbal memory span literature, Bopp and Verhaghen (2005) found that older adults show deficits across all aspects of verbal memory span, and that complex working memory span (CWKMS) tasks are more sensitive to these deficits than STM span tasks. This dissociation has been replicated several times and indicates that healthy older adults are not impaired in accessing or processing items held in the focus of attention, but do encounter difficulties in accessing and processing items which have been displaced from the focus (Basak & Verhaeghen, 2011). Interestingly, even though healthy older adults are not impaired at processing information stored within the focus, their accuracy is significantly impaired (Basak & Verhaeghen, 2011). One suggested possibility for this finding is that older adults have impaired attentional control abilities which results in a higher level of interference from items stored outside of the focus, and therefore reduced STM or WKM capacity. Basak and Verhaeghan (2011) note that this impairment is not necessarily due to WKM load, because during a random cue location n-back, performance did not decrease significantly as a function of increased load during non-switch location trials. They alternatively suggest that simultaneous storage and processing may be the detrimental factor in older adults' reduced WKM capacity.

Working memory in mild cognitive impairment

The global cognitive decline that begins upon conversion to AD manifests itself as increasingly prevalent deficits in activities of daily living and instrumental activities of daily living. The hallmark sign of these deficits in AD is impairment in LTM or episodic memory functioning. Accompanying the characteristic LTM deficit is also a severe impairment in WKM abilities (Baddeley et al., 2001; Belleville, Peretz, & Malenfant, 1996; Belleville et al., 2003; Kensinger et al., 2003). This is accompanied by deficits in attention and inhibition which can also be interpreted as contributing to WKM impairment (Amieva et al., 2004; Belleville, Chertkow, & Gauthier, 2007). Traditionally, it was thought that during the course of early AD only the episodic memory deficits were significant, but more recent studies have demonstrated that WKM deficits are also evident in the early stage of the disease (Germano & Kinsella, 2005). Similarly, various studies originally indicated that those with MCI primarily displayed deficits in episodic memory functioning (e.g., Jack et al., 1999; Kluger et al., 1999) and episodic memory deficits in those with a-MCI have been seen as most predictive of conversion to AD (Landau et al., 2010). Very few cognitive or neuropsychological test-based studies, though, have investigated WKM functioning in those with MCI (e.g., Alescio-Lautier et al., 2007; Belleville et al., 2007; Belleville et al., 2008; Gagnon & Belleville, 2011). Recent findings indicate consistent and significant impairments in attention, executive functioning, and WKM in both a-MCI and na-MCI (Saunders, 2011), while md-MCI patients exhibit the greatest impairment in WKM (Brandt et al., 2008). Belleville et al. (2007) observed that not only were MCI patients impaired on recall during a dual task, like the Brown-Peterson procedure, but were also impaired on recall when no

interference was presented. The latter indicates trouble maintaining items in the focus of attention, and may result from deficits in attention or other executive functions. In the only study to use CWKMS tasks on MCI, Gagnon and Belleville (2011) found that by varying the retention interval they could differentiate MCI-to-AD converters from non-converters, information not gleaned from the other neuropsychological measures which had been administered.

Neuroimaging

Functional neuroimaging of working memory

A significant drawback to solely relying on neuropsychological assessment for a diagnosis is that a subset of individuals experiencing mild cognitive impairment may not appear to significantly differ from controls. One reason for this possibility has already been discussed; individuals who naturally possess superior cognitive abilities may not be sufficiently impaired relative to controls. Another possibility is that compensatory brain mechanisms may be at work. In order to compensate for damage to task-relevant regions, those regions may need to be activated to a greater extent or the brain may even recruit alternative regions or pathways to achieve the desired response or output. The end result is a normal behavioral response which masks the underlying pathology. Evidence of such compensatory mechanisms, though, can be captured by functional neuroimaging as altered brain activity. Such neuroimaging biomarkers of neuropathology are extremely valuable because they may indicate which brain regions are malfunctioning or undergoing neurodegenerative processes. Given that WKM decline is evident in MCI and may actually precede episodic memory deficits, acquiring functional neuroimaging data

while MCI participants perform a WKM task may further elucidate how AD neuropathology initially manifests itself in the form of MCI.

Traditional neuroimaging WKM tasks such as the n-back and Sternberg task have provided valuable information regarding the regions typically involved in WKM in healthy adults (e.g., Braver et al., 1997; Derrfuss et al., 2004; Jonides et al., 1997; Knops et al., 2006; Owen et al., 2005; Schon et al., 2009). Regions believed to be integral to WKM processes are the DLPFC, VLPFC, ACC, IPL, SPL, precuneus, and the MTL (e.g., Axmacher et al., 2010; Cashdollar et al., 2009; Chein et al., 2011; Oztekin et al., 2009; for reviews see Blumenfeld & Ranganath, 2007; Bucci, 2009;Wager & Smith, 2003). As can be seen, this comprises a large portion of the brain, indicating that WKM is a complex cognitive process. The attributed functions of each of these regions, as elucidated by neuroimaging techniques, are described below. At a basic level, it is acknowledged that frontal, parietal, and MTL regions are part of a structured, highly interconnected network whose efficiency dictates the success of WKM processes and the resulting WKM capacity of an individual. The DLPFC is believed to be involved in attentional control (which may result in enhanced WKM capacity), the organizational processing of information, and the manipulation of information (e.g., Blumenfeld & Ranganath, 2006; Champod & Petrides, 2007; D'Esposito et al., 1999). The VLPFC / IFG is thought to be involved in the maintenance of spatial information, the rehearsal of verbal information, and the resolution of interference (Blumenfeld & Ranganath, 2007; Cabeza & Nyberg, 2000; Toepper et al. 2010). The ACC is relevant for cognitive control and may play an even greater role in executive functioning than the DLPFC (Kaneda & Osaka, 2008; Osaka et al., 2003; Smith & Jonides, 1999). The role of posterior parietal

cortex (PPC) in WKM is not as clear, but the SPL and precuneus are believed to store, maintain, and manipulate items residing in the focus of attention (Wager & Smith, 2003; Wendelken et al., 2008); the IPL, which has been shown to be a structural hub of the brain (Hagmann et al., 2008), may regulate the interactions between frontal and parietal regions. Lastly, parts of the MTLs are thought to regulate the maintenance and retrieval of items displaced from the focus of attention, possibly functioning as a storage buffer during WKM performance (Axmacher et al., 2009a, Axmacher at al., 2009b; Faraco et al., 2011).

Even though tasks such as the n-back have provided valuable insight about the regions involved in WKM, there are alternative tasks which may be better suited to examine WKM in older populations in a neuroimaging setting. In a sample that was not initially distinguishable on clinical neuropsychological measures, CWKMS tasks have been shown to differentiate between those with MCI who progressed to AD from those who did not (Gagnon & Belleville, 2011). A benefit of CWKMS tasks is that they continuously force to-be-remembered items to be displaced from the focus of attention and retrieved from LTM. This is important because neuroimaging technologies such as fMRI benefit from designs that quickly induce the highest amount of variability between conditions. The result is that all or most of the regions involved in WKM throughout task performance will be efficiently recruited during each block. Furthermore, CWKMS tasks have already been shown to be effective in eliciting activation in the above mentioned regions associated with WKM performance (Chein et al., 2010; Faraco et al., 2011; Kondo et al., 2005).

Functional neuroimaging of working memory in healthy older adults

Neuroimaging studies have found that older adults exhibit several different patterns of brain activity during various cognitive tasks, including WKM, in comparison to their young counterparts (Cabeza et al., 1997; Dew et al., 2011; Grady et al., 2002; Reuter-Lorenz et al., 2000; Spreng et al., 2010). One of the first theories to address these differences was the Hemispheric Asymmetries are Reduced in OLD (HAROLD; Cabeza, 2002; Cabeza et al., 2004) model. The HAROLD model is based on task related activations during a variety of tasks including WKM, episodic memory retrieval, and inhibitory control. In its most basic form, the HAROLD model states that older adults exhibit greater bilateral PFC activity during task performance than younger adults, and may even show an opposite pattern of activity as task difficulty increases compared to younger adults (e.g., greater right PFC activation as opposed to left PFC activation).

Some studies, though, have shown that at higher WKM loads younger adults also demonstrate bilateral recruitment (Mattay et al., 2006), and that bilateral activation in either group is not necessarily limited to PFC regions (Schneider-Garces et al., 2010). Mattay et al. (2006) also reported an inverted-U signal in the left PFC of younger adults in response to increasing n-back load, while the older adults only showed decreased bilateral PFC activation in response to n-back load; older adults exhibited greater bilateral activation during the 1-back though. Relatedly, Schneider-Garces et al. (2010) demonstrated that activation differences across younger and older adults can be accounted for solely as a matter of reduced WKM capacity. This supports the cognitive hypothesis that WKM performance differences between younger and older adults are the result of reduced WKM capacity in older adults, and supports the idea that individuals

will activate more cortical regions as task load increases, as hypothesized by the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz & Lustig, 2005).

Lastly, activation differences between older and younger adults may be explained by differences in cognitive control strategies, observed as temporal activation differences. Specifically, it is thought that older adults may be employing reactive rather than proactive strategies in response to probes and cues, which is seen as delayed activation in regions associated with successful task performance in younger adults. This pattern of activation can be described as an early-to-late shift in aging (ELSA) and has been observed in both PFC and medial temporal regions (Dew et al., 2011). Regardless of the particular model assumed when explaining signal differences between older and younger adults, older adults will exhibit differential activation in a variety of cortical regions. Depending on the task and load, activation differences may be observed as bilateral PFC activation, greater overall activity at low loads, reduced overall activation at high loads, or delayed activation as a result of shifts in cognitive strategies.

Functional neuroimaging of working memory in mild cognitive impairment

Previous neuroimaging studies of working or episodic memory in MCI patients have yielded mixed results. Even though a number of these studies find differences in frontal, parietal, and MTL regions, results are variable as to whether these ROIs are reported as displaying increased or decreased activation relative to the comparison group/s of interest, usually healthy adults or AD patients (e.g., Bokde et al., 2010; Hampstead et al., 2011; Kircher et al., 2007; Kochan et al., 2010; Kochan et al., 2011; Machulda et al., 2003; Yetkin et al., 2006). Overall, though, it appears the most

consistent finding is increased MTL activation compared to controls during a variety of memory tasks; this supports the idea that MCI patients are engaging compensatory mechanisms. In other words, because AD pathology is thought to initially have its most notable effects in the MTLs, increased activity in this region during initial neurodegeneration (during MCI) is thought to help maintain pre-morbid functioning. Longitudinal studies have even shown that increased hippocampal activity during memory tasks is predictive of incipient cognitive decline and should be used as a biomarker of MCI (Miller et al., 2008).

In one of the earliest fMRI memory studies on MCI, Machulda et al. (2003) found that during encoding of a visual scene, MCI and AD subjects displayed reduced MTL activation as compared to controls. MTL activation in the AD sample during encoding was found to be consistent with previous studies on AD, and is still consistent with current findings on AD encoding, but MCI findings are at odds with the current literature. For example, using a visual WKM paradigm with 2 probe images presented in 3-back fashion following the presentation of 4 novel images, Yetkin et al. (2006) found that MCI subjects exhibited greater right parahippocampal gyrus activation than AD patients and controls, while AD patients exhibited greater left parahippocampal gyrus activity than both MCI subjects and controls. Aside from the difference in task requirements, one explanation for the discrepancy in MTL in MCI activation was the subjects' abilities to perform the task. In Yetkin et al. (2006) there was no significant difference between the performance of control, MCI, and AD groups, while in Machulda et al. (2003) MCI and AD patients both performed significantly worse than controls. Therefore, careful

attention must be given to behavioral performance when interpreting findings of hypo- or hyper-activation in MCI.

In a verbal delayed match to sample task (Bokde et al., 2010), aMCI patients displayed greater frontal, temporal, and inferior parietal activation during encoding and maintenance compared to their performance matched controls, with the greatest differences occurring in frontal and temporal regions during maintenance. This indicates MCI subjects may have required greater neural resources to maintain information. Interestingly, reaction time during the recall phase was positively correlated with left hippocampal activation during recall for the MCI patients, but with left hippocampal activation during encoding for the controls. Similarly, Hampstead et al. (2011) detected an overall reduction of brain activity, including the MTLs, in MCI subjects during encoding/storing of object-location associations. This suggests that healthy older adults are successfully encoding and storing information, and can easily access the information during recall, while those with MCI are not and require greater resources to recall that information. Furthermore, Bokde et al. (2010) demonstrated that regions activated across all three phases (encoding, maintenance, and recall) were more similar for the MCI group than controls. The authors suggest that along with the fact those with MCI did not recruit DLPFC throughout the task, as opposed to controls, these findings further support the idea that impaired WKM functioning in MCI may result from impaired executive abilities.

Kochan and colleagues (2010; 2011) have suggested the use of load-varied functional activation patterns in regions other than the MTLs as a biomarker for MCI. Kochan et al. (2010) indicated that community dwelling MCI subjects show increased

activation in the ACC and precuneus during the encoding phase of the lower load conditions as compared to healthy older adults. During the high load condition MCI subjects displayed decreased activation in these regions during encoding as compared to healthy older adults, and demonstrated a greater degree of hypoactivation in a posterior cingulate – medial precuneus region as compared to healthy older adults. In an ROI analysis, Kochan et al. (2011) further demonstrated that greater load induced deactivation in the posteromedial cortex (medial precuneus, posterior cingulate, and retrosplenial cortex) significantly predicted functional decline in activities of daily living for MCI subjects over a 2-year period. This result remained significant after controlling for baseline clinical and functional status, MCI subtype, APOE allele type, and grey matter and hippocampal volumes (factors indicative of MCI decline). It should be noted that reduced accuracy at high load was an independent predictor of decline.

Diffusion tensor imaging

Briefly, DTI is a form of diffusion weighted (DW) imaging that acquires DW images along various orientations in order to calculate a tensor describing the diffusion of water along three principal axes (e.g., Melhem et al., 2002). Being that the diffusion of water is affected by the properties of the surrounding environment, DW modalities such as DTI are well suited to describe such properties; in neuroimaging it is best suited to describe the white matter (WM), or fiber bundles, of the brain. In the brain it is believed the greatest impact on diffusion may occur due to the tight packing of fibers and the inherent properties of the cell membranes (Beaulieu, 2002). Through various combinations of the eigenvalues ($\lambda 1$, $\lambda 2$, and $\lambda 3$), which describe the strength of diffusion along the corresponding axis or eigenvector (v1, v2, and v3), several scalar indices of

diffusion can be calculated which are thought to describe different properties of the surrounding WM.

Axial diffusivity (DA) describes the principal eigenvalue (λ1) and is assumed to contribute information regarding the integrity of axons (Glenn et al., 2003) or changes in extra-axonal/extracellular space (Beaulieu and Allen, 1994). In contrast, radial diffusivity (DR) is the average of the two other eigenvalues ([λ2+λ3]/2) and is assumed to characterize changes associated with myelination or glial cell morphology (Song et al., 2002, 2003, 2005). Mean diffusivity (MD) is the average of all three eigenvalues and provides an all-round descriptor of the degree of diffusivity within the region, where increased diffusivity may indicate decreased WM integrity. Lastly, fractional anisotropy (FA) indicates how biased, or anisotropic, diffusion is along the primary eigenvector. In other words, FA is the ratio of the tensor's anisotropy to the whole tensor (Melhem et al., 2002), and is used as an index of overall WM health or integrity (Beaulieu et al., 1996), with reduced anisotropy also being indicative of reduced WM integrity. MD and FA though, can be greatly affected in regions where there are crossing fibers (Alexander et al., 2007; Vos et al., 2012), thereby providing an inaccurate description of local diffusion characteristics

Diffusion tensor imaging in healthy older adults

Evidence of aging-associated brain deterioration due to myelin degeneration has been found in both non-human primates and humans (Peters et al., 2000; Yakovlev & Lecours, 1967). It also appears that most of the age-related myelin degeneration occurs in the frontal lobes, with a spatial gradient of increasing degeneration from posterior to

frontal regions (Kinney et al., 1988; Sakuma et al., 1991). Several DTI studies have provided support for this idea. Head et al. (2004) reported that healthy older adults had decreased FA and increased MD compared to healthy young adults in the anterior and posterior portions of the corpus callosum, with the anterior callosum exhibiting significantly greater FA and MD changes. They also reported significant FA and MD changes in the frontal, temporal, parietal, and occipital lobes of older adults, with significantly greater FA and MD differences in the frontal lobes and the smallest differences occurring in the occipital lobes. Similarly, Pfeffebaum et al. (2005) demonstrated that older adults, as compared to young adults, had significantly more regions of reduced FA in frontal regions than posterior regions, in both slice-by-slice profile and ROI analyses. Recently, Davis et al. (2009) showed further support for the idea of a posterior-anterior gradient of myelin degeneration by demonstrating FA differences across longitudinal pathways that strictly course through the frontal and parietal lobes. Specifically, significantly greater differences were evidenced along a posterior-anterior gradient in the uncinate fasciculus and cingulated bundle, both of which displayed initial group FA differences.

Diffusion tensor imaging in mild cognitive impairment

WM damage as a result of AD has been well documented through postmortem examinations, MRI, and volumetric measures (Gold et al., 2007; Kavcic et al., 2008; Rose et al., 2008; Salat et al., 2009; Yasmin et al., 2008) within various regions, including the frontal, temporal, and parietal lobes, and the hippocampus; and across various fiber bundles including the posterior cingulum, uncinate fasciculus, superior longitudinal fasciculus, and splenium and genu of the corpus callosum (Sexton et al.,

2011). The differences between MCI and controls and between MCI and AD are much less clear and tend to be variable (Sexton et al., 2011), possibly reflecting the heterogeneous nature of the condition. A meta-analysis of DTI studies on MCI and AD populations which only used ROI based analysis detected large effect sizes for increased MD in the hippocampus and parietal lobes and decreased hippocampal FA for MCI individuals compared to controls (Sexton et al., 2011). It should be noted that a significant degree of heterogeneity was detected in 5 out of 13 group comparisons for FA in AD and 7 out of 9 group comparisons for FA in MCI; MD only displayed a significant heterogeneity for 3 out of 8 comparisons for MCI. Such findings not only highlight the fact that MCI is a neurodegeneratively heterogeneous condition, but also point out the variability inherent to measures such as FA.

Increased diffusivity in the hippocampus, as measured by MD, and decreased hippocampal volume have been shown to be predictive of progression to AD for individuals with aMCI (Schroeter, 2009). Interestingly, adding MD values to a hippocampal volume model predicting conversion to AD was shown to increase prognostic accuracy, but the converse was not true. This indicates that hippocampal MD values may be a better predictor of conversion to AD than some methods of volumetric hippocampal measurement (Kantarci et al., 2005). Additionally, MTL indices may differentiate aMCI from naMCI. Both increased MD in the hippocampus (Kantarci et al., 2009) and reduced FA in the fornix (Zhuang et al., 2010) have been demonstrated in aMCI when compared to controls, but not in naMCI. Such findings are in agreement with the idea that aMCI is most prognostic of conversion to AD, commonly associated with damage to the MTLs. No significant predictors discriminated between naMCI and

controls. When compared to each other aMCI and naMCI did not show any differences in FA values. Pievani et al. (2010) also found significant tract damage in the fornix and the cingulum bundle in MCI patients. Limbic tract damage may be due to secondary degeneration and myelin damage as indicated by a greater increase in DR as opposed to DA. The authors suggest that DA and DR may be potential early biomarkers for AD WM pathology, since various other studies have reported non-significant differences in FA and/or MD between MCI subjects and controls.

It appears that even though MD and FA are the two mostly commonly used indices of diffusion, these two indices, but especially FA, can be problematic because they are calculated from all three eigenvalues. Previous work has shown that WM changes in early AD are likely to produce proportional changes along all three eigenvectors as FA was grossly insensitive to changes that were evidenced through analysis of DA, DR, and MD (Acosta-Cabronero et al., 2010). Furthermore, Bosch et al. (2012) found that DR and MD were sensitive to WM changes in AD and aMCI in regions where FA differences were not detected. Therefore it appears that DTI studies of microstructural WM changes in MCI may be best served by examining diffusivity measures rather than FA.

To gain additional insight into the implications of neurodegeneration in MCI and AD, associations between indices of WM degeneration and cognition should be established. Currently, correlations between cognitive performance and DTI measures have been explored a handful of times (e.g., Bosch et al., 2012; Fjell 2009; Heo 2009). Most of these studies have used the Mini Mental State Examination (MMSE; Folstein et al., 1975), a brief questionnaire designed to assess various aspects of cognition. Even

though the MMSE is commonly used in clinical practice to identify AD, it is not as sensitive to MCI (Nasreddine et al., 2005; Tomabaugh et al., 1992; Wind et al., 1997). Despite the fact that AD and MCI deficit are traditionally associated with a deficit of episodic memory (Welsh et al., 1991; 1992), recent evidence suggests that episodic deficits may actually be preceded by more subtle changes in cognition due to impaired language, attentional, executive functioning, and WKM abilities (Cuetos et al., 2007; Grober et al., 2008; Rapp & Reischies, 2005; Storandt, 2008), and that deficits in these domains are actually characteristic of preclinical AD (Twamley et al., 2006).

Aims

This study had two primary aims. The first aim was to examine whether CWKMS tasks may serve as suitable neuroimaging paradigms to discover functional endophenotypic markers of MCI. Behavioral results from CWKMS tasks have already been shown to discriminate between young and older adults (Bopp & Verhaghen, 2005), as well as MCI converters from non-converters (Gagnon and Belleville, 2011). The current study used a multi-modal CWKMS task composed of a visuo-spatial attention task and a verbal STM task, similar in concept to that used by Chein et al. (2010). This causes the visuo-spatial task to act as a distractor task and effectively forces the to-be-remembered letters from the verbal STM task to be displaced from the focus of attention, recruiting LTM mechanisms. The constituent tasks were also presented independently.

We expected that if groups performed equally, the MCI group would exhibit greater activation during encoding and maintenance in the frontal and medial temporal lobes. This hypothesis is based on the fact that MCI patients show deficits in LTM

functioning, often associated with MTL dysfunction, and have been shown to display significant executive deficits (Grober et al., 2008; Rapp et al., 2005; Saunders & Summers, 2011), often associated with frontal regions (Grambaite et al., 2011). Increased activation would be consistent with compensatory views of functional activation and with the fact that MCI patients often exhibit WM-related differences across many of these regions. Following Kochan et al. (2010), who had MCI patients perform a graded WM challenge, it was expected that participants with MCI would also exhibit reduced PPC activation in comparison to healthy older adults during encoding and maintenance due to the high load induced by the CWKMS task. The use of CWKMS tasks during functional imaging of MCI is a novel endeavor and may also reveal novel patterns or biomarkers of functional activation in those with MCI. Lastly, we also hypothesized that the MCI group would exhibit significantly greater activation in the MTLs and PFC during CWKMS recall.

The second aim of the current study was to examine whether different cognitive processes as measured by RBANS index scores were sensitive to WM degeneration occurring in MCI. Based on the cognitive impairments evidenced in MCI, it was expected that immediate memory (IM), delayed memory (DM), attention (ATT), and language (LAN) scores will be correlated with diffusivity indices (DA, DR, and MD) in areas of WM degeneration. Specifically: 1) Diffusivity indices of the hippocampus should negatively correlate with DM scores. 2) DM, IM, and ATT indices, whose sub-tests all appear to rely on some aspect of WKM functioning, will likely be negatively correlated with diffusivity indices in fasciculi connecting frontal and parietal cortices, as these regions are typically associated with WKM functioning (Badre & Wagner, 2007;

Buckner & Wheeler, 2001; Cavanna & Trimble, 2006; Wager & Smith, 2003). The most prominent fasciculi extending between these regions are the superior longitudinal fasciculus (SLF) and the fronto-occipital fasciculus (FOF). 3) LAN scores, which are heavily dependent of semantic fluency, will likely be negatively correlated with WM diffusivity indices in WM pathways coursing through the temporal lobe, as it is involved in speech production, language processing, and object fluency (Fama et al., 2000; Hickok, 2001; Hickok, 2009; Levelt et al., 1998).

References

Akiyama, H., Meyer, J.S., Mortel, K.F., Terayama, Y., Thornby, J.I., Konno, S., 1997. Normal human aging: factors contributing to cerebral atrophy. J Neurol Sci 152, 39-49.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 270-279.

Alescio-Lautier, B., Michel, B.F., Herrera, C., Elahmadi, A., Chambon, C., Touzet, C., Paban, V., 2007. Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention. Neuropsychologia 45, 1948-1960.

Alexander, A.L., Lee, J.E., Lazar, M., Field, A.S., 2007. Diffusion tensor imaging of the brain. Neurotherapeutics 4, 316-329.

Amieva, H., Phillips, L.H., Della Sala, S., Henry, J.D., 2004. Inhibitory functioning in Alzheimer's disease. Brain 127, 949-964.

Axmacher, N., Elger, C.E., Fell, J., 2009. Working memory-related hippocampal deactivation interferes with long-term memory formation. J Neurosci 29, 1052-1960.

Axmacher, N., Haupt, S., Cohen, M.X., Elger, C.E., Fell, J., 2009. Interference of working memory load with long-term memory formation. Eur J Neurosci 29, 1501-1513.

Axmacher, N., Lenz, S., Haupt, S., Elger, C.E., Fell, J., 2010. Electrophysiological signature of working and long-term memory interaction in the human hippocampus. Eur J Neurosci 31, 177-188.

Baddeley, A., 2000. The episodic buffer: a new component of working memory? Trends Cogn Sci 4, 417-423.

Baddeley, A.D., Baddeley, H.A., Bucks, R.S., Wilcock, G.K., 2001. Attentional control in Alzheimer's disease. Brain 124, 1492-1508.

Baddeley, A.D., Hitch, G., 1974. Working Memory. In: Bower, G.H. (Ed.), The psychology of learning and motivation: Advances in research and theory. Academic Press, New York, pp. 47-89.

Badre, D., Wagner, A.D., 2007. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia 45, 2883-2901.

Basak, C., Verhaeghen, P., 2011. Aging and switching the focus of attention in working memory: age differences in item availability but not in item accessibility. J Gerontol B Psychol Sci Soc Sci 66, 519-526.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed 15, 435-455.

Beaulieu, C., Allen, P.S., 1994. Determinants of anisotropic water diffusion in nerves. Magn Reson Med 31, 394-400.

Beaulieu, C., Does, M.D., Snyder, R.E., Allen, P.S., 1996. Changes in water diffusion due to Wallerian degeneration in peripheral nerve. Magn Reson Med 36, 627-631.

Belleville, S., Chertkow, H., Gauthier, S., 2007. Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. Neuropsychology 21, 458-469.

Belleville, S., Peretz, I., Malenfant, D., 1996. Examination of the working memory components in normal aging and in dementia of the Alzheimer type. Neuropsychologia 34, 195-207.

Belleville, S., Rouleau, N., Van der Linden, M., Collette, F., 2003. Effect of manipulation and irrelevant noise on working memory capacity of patients with Alzheimer's dementia. Neuropsychology 17, 69-81.

Belleville, S., Sylvain-Roy, S., de Boysson, C., Menard, M.C., 2008. Characterizing the memory changes in persons with mild cognitive impairment. Prog Brain Res 169, 365-375.

Blumenfeld, R.S., Ranganath, C., 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci 26, 916-925.

Blumenfeld, R.S., Ranganath, C., 2007. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist 13, 280-291.

Bokde, A.L., Karmann, M., Born, C., Teipel, S.J., Omerovic, M., Ewers, M., Frodl, T., Meisenzahl, E., Reiser, M., Moller, H.J., Hampel, H., 2010. Altered brain activation during a verbal working memory task in subjects with amnestic mild cognitive impairment. J Alzheimers Dis 21, 103-118.

Bopp, K.L., Verhaeghen, P., 2005. Aging and verbal memory span: a meta-analysis. J Gerontol B Psychol Sci Soc Sci 60, P223-233.

Bosch, B., Arenaza-Urquijo, E.M., Rami, L., Sala-Llonch, R., Junque, C., Sole-Padulles, C., Pena-Gomez, C., Bargallo, N., Molinuevo, J.L., Bartres-Faz, D., 2012. Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. Neurobiol Aging 33, 61-74.

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5, 49-62.

Broadbent, D.E., 1958. Perception and communication. Pergamon Press, London.

Bucci, D.J., 2009. Posterior parietal cortex: an interface between attention and learning? Neurobiol Learn Mem 91, 114-120.

Buckner, R.L., Wheeler, M.E., 2001. The cognitive neuroscience of remembering. Nat Rev Neurosci 2, 624-634.

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging 17, 85-100.

Cabeza, R., Daselaar, S.M., Dolcos, F., Prince, S.E., Budde, M., Nyberg, L., 2004. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex 14, 364-375.

Cabeza, R., Grady, C.L., Nyberg, L., McIntosh, A.R., Tulving, E., Kapur, S., Jennings, J.M., Houle, S., Craik, F.I., 1997. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. J Neurosci 17, 391-400.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12, 1-47.

Cashdollar, N., Malecki, U., Rugg-Gunn, F.J., Duncan, J.S., Lavie, N., Duzel, E., 2009. Hippocampus-dependent and -independent theta-networks of active maintenance. Proc Natl Acad Sci U S A 106, 20493-20498.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564-583.

Champod, A.S., Petrides, M., 2007. Dissociable roles of the posterior parietal and the prefrontal cortex in manipulation and monitoring processes. Proc Natl Acad Sci U S A 104, 14837-14842.

Chein, J.M., Moore, A.B., Conway, A.R., 2011. Domain-general mechanisms of complex working memory span. Neuroimage 54, 550-559.

Christensen, H., 2001. What cognitive changes can be expected with normal ageing? Aust N Z J Psychiatry 35, 768-775.

Clark, J.H., Hobson, V.L., O'Bryant, S.E., 2010. Diagnostic accuracy of percent retention scores on RBANS verbal memory subtests for the diagnosis of Alzheimer's disease and mild cognitive impairment. Arch Clin Neuropsychol 25, 318-326.

Cowan, N., 1988. Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system. Psychol Bull 104, 163-191.

Cowan, N., 1999. Mechanisms of active maintenance and executive control. In: Miyake, A., Shah, P. (Eds.), Models of Working Memory. Cambridge University Press, Cambridge, pp. 61-101.

Cowan, N., 2001. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. Behav Brain Sci 24, 87-114; discussion 114-185.

Cowan, N., 2005. Working memory capacity. Psychology Press, New York.

Crook, T., Bartus, R.T., Ferris, S.H., Whitehouse, P., Cohen, G.D., Gershon, S., 1986. Age associated memory impairment: Proposed diagnostic criteria and measures of clinical change - report of a National Institute of Mental Health work group. Developmental Neuropsychology 2, 261-276.

Davis, S.W., Dennis, N.A., Buchler, N.G., White, L.E., Madden, D.J., Cabeza, R., 2009. Assessing the effects of age on long white matter tracts using diffusion tensor tractography. Neuroimage 46, 530-541.

De Jager, C.A., Hogervorst, E., Combrinck, M., Budge, M.M., 2003. Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. Psychol Med 33, 1039-1050.

DeCarli, C., 2003. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2, 15-21.

Derrfuss, J., Brass, M., von Cramon, D.Y., 2004. Cognitive control in the posterior frontolateral cortex: evidence from common activations in task coordination, interference control, and working memory. Neuroimage 23, 604-612.

D'Esposito, M., Postle, B.R., Ballard, D., Lease, J., 1999. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cogn 41, 66-86.

Dew, I.T., Buchler, N., Dobbins, I.G., Cabeza, R., 2011. Where Is ELSA? The Early to Late Shift in Aging. Cereb Cortex.

Duff, K., Hobson, V.L., Beglinger, L.J., O'Bryant, S.E., 2010. Diagnostic accuracy of the RBANS in mild cognitive impairment: limitations on assessing milder impairments. Arch Clin Neuropsychol 25, 429-441.

Duff, K., Humphreys Clark, J., O'Bryant, S., Mold, J., Schiffer, R., Sutker, P., 2008. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. Archives of Clinical Neuropsychology 23, 603-612.

Engle, R.W., Kane, M.J., Tuholski, S.W., 1999. Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In: Miyake, A., Shah, P. (Eds.), Models of working memory. Cambridge University Press, Cambridge, pp. 102-134.

Fama, R., Sullivan, E.V., Shear, P.K., Cahn-Weiner, D.A., Marsh, L., Lim, K.O., Yesavage, J.A., Tinklenberg, J.R., Pfefferbaum, A., 2000. Structural brain correlates of verbal and nonverbal fluency measures in Alzheimer's disease. Neuropsychology 14, 29-40.

Faraco, C.C., Unsworth, N., Langley, J., Terry, D., Li, K., Zhang, D., Liu, T., Miller, L.S., 2011. Complex span tasks and hippocampal recruitment during working memory. Neuroimage 55, 773-787.

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., Krampla, W., Tragl, K.H., 2007. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. Neurology 68, 288-291.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. J Neurosci 29, 15223-15231.

Fjell, A.M., Westlye, L.T., Espeseth, T., Reinvang, I., Dale, A.M., Holland, D., Walhovd, K.B., 2010. Cortical gray matter atrophy in healthy aging cannot be explained by undetected incipient cognitive disorders: a comment on Burgmans et al. (2009). Neuropsychology 24, 258-263; discussion 264-266.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12, 189-198.

Fox, N.C., Schott, J.M., 2004. Imaging cerebral atrophy: normal ageing to Alzheimer's disease. Lancet 363, 392-394.

Germano, C., Kinsella, G.J., 2005. Working memory and learning in early Alzheimer's disease. Neuropsychol Rev 15, 1-10.

Glenn, O.A., Henry, R.G., Berman, J.I., Chang, P.C., Miller, S.P., Vigneron, D.B., Barkovich, A.J., 2003. DTI-based three-dimensional tractography detects differences in the pyramidal tracts of infants and children with congenital hemiparesis. J Magn Reson Imaging 18, 641-648.

Gold, G., Giannakopoulos, P., Herrmann, F.R., Bouras, C., Kovari, E., 2007. Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain 130, 2830-2836.

Grady, C.L., Bernstein, L.J., Beig, S., Siegenthaler, A.L., 2002. The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. Psychol Aging 17, 7-23.

Grambaite, R., Selnes, P., Reinvang, I., Aarsland, D., Hessen, E., Gjerstad, L., Fladby, T., 2011. Executive dysfunction in mild cognitive impairment is associated with changes in frontal and cingulate white matter tracts. J Alzheimers Dis 27, 453-462.

Grober, E., Hall, C.B., Lipton, R.B., Zonderman, A.B., Resnick, S.M., Kawas, C., 2008. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Int Neuropsychol Soc 14, 266-278.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol 6, e159.

Hamalainen, A., Grau-Olivares, M., Tervo, S., Niskanen, E., Pennanen, C., Huuskonen, J., Kivipelto, M., Hanninen, T., Tapiola, M., Vanhanen, M., Hallikainen, M., Helkala, E.L., Nissinen, A., Vanninen, R.L., Soininen, H., 2008. Apolipoprotein E epsilon 4 allele is associated with increased atrophy in progressive mild cognitive impairment: a voxel-based morphometric study. Neurodegener Dis 5, 186-189.

Hampstead, B.M., Stringer, A.Y., Stilla, R.F., Amaraneni, A., Sathian, K., 2011. Where did I put that? Patients with amnestic mild cognitive impairment demonstrate widespread reductions in activity during the encoding of ecologically relevant object-location associations. Neuropsychologia 49, 2349-2361.

He, J., Farias, S., Martinez, O., Reed, B., Mungas, D., Decarli, C., 2009. Differences in brain volume, hippocampal volume, cerebrovascular risk factors, and

apolipoprotein E4 among mild cognitive impairment subtypes. Arch Neurol 66, 1393-1399.

He, X., Cooley, K., Chung, C.H., Dashti, N., Tang, J., 2007. Apolipoprotein receptor 2 and X11 alpha/beta mediate apolipoprotein E-induced endocytosis of amyloid-beta precursor protein and beta-secretase, leading to amyloid-beta production. J Neurosci 27, 4052-4060.

Head, D., Buckner, R.L., Shimony, J.S., Williams, L.E., Akbudak, E., Conturo, T.E., McAvoy, M., Morris, J.C., Snyder, A.Z., 2004. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cereb Cortex 14, 410-423.

Hickok, G., 2001. Functional anatomy of speech perception and speech production: psycholinguistic implications. J Psycholinguist Res 30, 225-235.

Hickok, G., 2009. The functional neuroanatomy of language. Phys Life Rev 6, 121-143.

Jack, C.R., Jr., Petersen, R.C., Xu, Y.C., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Waring, S.C., Tangalos, E.G., Kokmen, E., 1999. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 52, 1397-1403.

Johnson, V.E., Stewart, W., Smith, D.H., 2012. Widespread tau and amyloid-Beta pathology many years after a single traumatic brain injury in humans. Brain Pathol 22, 142-149.

Jonides, J., Schumacher, E.H., Smith, E.E., 1997. Verbal working memory load affects regional brain activation as measured by PET. J Cogn Neurosci 9, 462-475.

Kaneda, M., Osaka, N., 2008. Role of anterior cingulate cortex during semantic coding in verbal working memory. Neurosci Lett 436, 57-61.

Kantarci, K., Avula, R.T., Senjem, L.M., Samikoglu, A.R., Shiung, M.M., Przybelski, S.A., Weigand, S.D., Ward, H.A., Vemuri, P., Knopman, D.S., Boeve, B.F., Petersen, R.C., Jack Jr., C.R., 2009. Diffusion tensor imaging characteristics of amnestic and nonamnestic mild cognitive impairment. Alzheimer's & Dementia 5, P12.

Kantarci, K., Petersen, R.C., Boeve, B.F., Knopman, D.S., Weigand, S.D., O'Brien, P.C., Shiung, M.M., Smith, G.E., Ivnik, R.J., Tangalos, E.G., Jack, C.R., Jr., 2005. DWI predicts future progression to Alzheimer disease in amnestic mild cognitive impairment. Neurology 64, 902-904.

Kavcic, V., Ni, H., Zhu, T., Zhong, J., Duffy, C.J., 2008. White matter integrity linked to functional impairments in aging and early Alzheimer's disease. Alzheimers Dement 4, 381-389.

Kensinger, E.A., Shearer, D.K., Locascio, J.J., Growdon, J.H., Corkin, S., 2003. Working memory in mild Alzheimer's disease and early Parkinson's disease. Neuropsychology 17, 230-239.

Kinney, H.C., Brody, B.A., Kloman, A.S., Gilles, F.H., 1988. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. J Neuropathol Exp Neurol 47, 217-234.

Kircher, T.T., Weis, S., Freymann, K., Erb, M., Jessen, F., Grodd, W., Heun, R., Leube, D.T., 2007. Hippocampal activation in patients with mild cognitive impairment is

necessary for successful memory encoding. J Neurol Neurosurg Psychiatry 78, 812-818.

Kluger, A., Ferris, S.H., Golomb, J., Mittelman, M.S., Reisberg, B., 1999. Neuropsychological prediction of decline to dementia in nondemented elderly. J Geriatr Psychiatry Neurol 12, 168-179.

Knops, A., Nuerk, H.C., Fimm, B., Vohn, R., Willmes, K., 2006. A special role for numbers in working memory? An fMRI study. Neuroimage 29, 1-14.

Kochan, N.A., Breakspear, M., Slavin, M.J., Valenzuela, M., McCraw, S., Brodaty, H., Sachdev, P.S., 2010. Functional alterations in brain activation and deactivation in mild cognitive impairment in response to a graded working memory challenge. Dement Geriatr Cogn Disord 30, 553-568.

Kochan, N.A., Breakspear, M., Valenzuela, M., Slavin, M.J., Brodaty, H., Wen, W., Trollor, J.N., Turner, A., Crawford, J.D., Sachdev, P.S., 2011. Cortical responses to a graded working memory challenge predict functional decline in mild cognitive impairment. Biol Psychiatry 70, 123-130.

Kondo, H., Morishita, M., Osaka, N., Osaka, M., Fukuyama, H., Shibasaki, H., 2004. Functional roles of the cingulo-frontal network in performance on working memory. Neuroimage 21, 2-14.

Landau, S.M., Harvey, D., Madison, C.M., Reiman, E.M., Foster, N.L., Aisen, P.S., Petersen, R.C., Shaw, L.M., Trojanowski, J.Q., Jack, C.R., Jr., Weiner, M.W., Jagust, W.J., 2010. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 75, 230-238.

Levelt, W.J., Praamstra, P., Meyer, A.S., Helenius, P., Salmelin, R., 1998. An MEG study of picture naming. J Cogn Neurosci 10, 553-567.

Libon, D.J., McMillan, C., Gunawardena, D., Powers, C., Massimo, L., Khan, A., Morgan, B., Farag, C., Richmond, L., Weinstein, J., Moore, P., Coslett, H.B., Chatterjee, A., Aguirre, G., Grossman, M., 2009. Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. Neurology 73, 535-542.

Luo, L., Craik, F.I., 2008. Aging and memory: a cognitive approach. Can J Psychiatry 53, 346-353.

Machulda, M.M., Ward, H.A., Borowski, B., Gunter, J.L., Cha, R.H., O'Brien, P.C., Petersen, R.C., Boeve, B.F., Knopman, D., Tang-Wai, D.F., Ivnik, R.J., Smith, G.E., Tangalos, E.G., Jack, C.R., Jr., 2003. Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. Neurology 61, 500-506.

Mattay, V.S., Fera, F., Tessitore, A., Hariri, A.R., Berman, K.F., Das, S., Meyer-Lindenberg, A., Goldberg, T.E., Callicott, J.H., Weinberger, D.R., 2006. Neurophysiological correlates of age-related changes in working memory capacity. Neurosci Lett 392, 32-37.

Mayr, U., Kliegl, R., 1993. Sequential and coordinative complexity: age-based processing limitations in figural transformations. J Exp Psychol Learn Mem Cogn 19, 1297-1320.

McElree, B., 2001. Working memory and focal attention. J Exp Psychol Learn Mem Cogn 27, 817-835.

McElree, B., 2006. Accessing recent events. In: Ross, B.H. (Ed.), The psychology of learning and motivation. Academic Press, San Diego.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34, 939-944.

Melhem, E.R., Mori, S., Mukundan, G., Kraut, M.A., Pomper, M.G., van Zijl, P.C., 2002. Diffusion tensor MR imaging of the brain and white matter tractography. AJR Am J Roentgenol 178, 3-16.

Miller, S.L., Fenstermacher, E., Bates, J., Blacker, D., Sperling, R.A., Dickerson, B.C., 2008. Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline. J Neurol Neurosurg Psychiatry 79, 630-635.

Milner, B., 1972. Disorders of learning and memory after temporal lobe lesions in man. Clin Neurosurg 19, 421-446.

Mitchell, A.J., Shiri-Feshki, M., 2009. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 119, 252-265.

Okonkwo, O.C., Alosco, M.L., Jerskey, B.A., Sweet, L.H., Ott, B.R., Tremont, G., 2010. Cerebral atrophy, apolipoprotein E varepsilon4, and rate of decline in everyday function among patients with amnestic mild cognitive impairment. Alzheimers Dement 6, 404-411.

Osaka, M., Osaka, N., Kondo, H., Morishita, M., Fukuyama, H., Aso, T., Shibasaki, H., 2003. The neural basis of individual differences in working memory capacity: an fMRI study. Neuroimage 18, 789-797.

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25, 46-59.

Oztekin, I., McElree, B., Staresina, B.P., Davachi, L., 2009. Working memory retrieval: contributions of the left prefrontal cortex, the left posterior parietal cortex, and the hippocampus. J Cogn Neurosci 21, 581-593.

Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., 2002. Models of Visuospatial and Verbal Memory Across the Adult Life Span. Psychology and Aging 17, 299-320.

Peters, A., Moss, M.B., Sethares, C., 2000. Effects of aging on myelinated nerve fibers in monkey primary visual cortex. J Comp Neurol 419, 364-376.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J Intern Med 256, 183-194.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., Winblad, B., 2001. Current concepts in mild cognitive impairment. Arch Neurol 58, 1985-1992.

Petersen, R.C., Ivnik, R.J., Boeve, B.F., Knopman, D.S., Smith, G.E., Tangalos, E.G., 2004. Outcome of clinical subtypes of mild cognitive impairment. Neurology (abstract) 62, A29S.

Petersen, R.C., Morris, J.C., 2005. Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 62, 1160-1163; discussion 1167.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56, 303-308.

Pfefferbaum, A., Adalsteinsson, E., Sullivan, E.V., 2005. Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. Neuroimage 26, 891-899.

Pievani, M., Agosta, F., Pagani, E., Canu, E., Sala, S., Absinta, M., Geroldi, C., Ganzola, R., Frisoni, G.B., Filippi, M., 2010. Assessment of white matter tract damage in mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 31, 1862-1875.

Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D.R., Ofstedal, M.B., Burke, J.R., Hurd, M.D., Potter, G.G., Rodgers, W.L., Steffens, D.C., Willis, R.J., Wallace, R.B., 2007. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 29, 125-132.

Pratt, M.W., Boyes, C., Robins, S., Mancester, J., 1989. Telling tales: Aging, working memory, and the narrative cohesion of story retellings. Developmental Psychology 25, 628-635.

Randolph, C., 1998. Repeatable battery for the assessment of neuropsychological status. The Psychological Corporation, San Antonio, Tx.

Rapp, M.A., Reischies, F.M., 2005. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). Am J Geriatr Psychiatry 13, 134-141.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex 15, 1676-1689.

Resnick, S.M., Pham, D.L., Kraut, M.A., Zonderman, A.B., Davatzikos, C., 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 23, 3295-3301.

Reuter-Lorenz, P.A., Jonides, J., Smith, E.E., Hartley, A., Miller, A., Marshuetz, C., Koeppe, R.A., 2000. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 12, 174-187.

Reuter-Lorenz, P.A., Lustig, C., 2005. Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol 15, 245-251.

Roach, E.S., 2005. Treating mild cognitive impairment: The absence of evidence. Archives of Neurology 62, 1167.

Rose, S.E., Janke, A.L., Chalk, J.B., 2008. Gray and white matter changes in Alzheimer's disease: a diffusion tensor imaging study. J Magn Reson Imaging 27, 20-26.

Rountree, S.D., Waring, S.C., Chan, W.C., Lupo, P.J., Darby, E.J., Doody, R.S., 2007. Importance of subtle amnestic and nonamnestic deficits in mild cognitive impairment: prognosis and conversion to dementia. Dement Geriatr Cogn Disord 24, 476-482.

Sakuma, H., Nomura, Y., Takeda, K., Tagami, T., Nakagawa, T., Tamagawa, Y., Ishii, Y., Tsukamoto, T., 1991. Adult and neonatal human brain: diffusional anisotropy and myelination with diffusion-weighted MR imaging. Radiology 180, 229-233.

Salat, D.H., Greve, D.N., Pacheco, J.L., Quinn, B.T., Helmer, K.G., Buckner, R.L., Fischl, B., 2009. Regional white matter volume differences in nondemented aging and Alzheimer's disease. Neuroimage 44, 1247-1258.

Salthouse, T.A., 1992. Influence of processing speed on adult age differences in working memory. Acta Psychol (Amst) 79, 155-170.

Salthouse, T.A., 1994. The aging of working memory. Neuropsychology 8, 535-543.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol Rev 103, 403-428.

Salthouse, T.A., 2000. Aging and measures of processing speed. Biol Psychol 54, 35-54.

Salthouse, T.A., Babcock, R.L., 1991. Decomposing adult age differences in working memory. Developmental Psychology 27, 763-776.

Salthouse, T.A., Lichty, W., 1985. Tests of the neural noise hypothesis of age-related cognitive change. J Gerontol 40, 443-450.

Saunders, N.L., Summers, M.J., 2010. Attention and working memory deficits in mild cognitive impairment. J Clin Exp Neuropsychol 32, 350-357.

Saunders, N.L., Summers, M.J., 2011. Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. Neuropsychology 25, 237-248.

Schneider-Garces, N.J., Gordon, B.A., Brumback-Peltz, C.R., Shin, E., Lee, Y., Sutton, B.P., Maclin, E.L., Gratton, G., Fabiani, M., 2010. Span, CRUNCH, and beyond: working memory capacity and the aging brain. J Cogn Neurosci 22, 655-669.

Schroeter, M.L., Stein, T., Maslowski, N., Neumann, J., 2009. Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 47, 1196-1206.

Sexton, C.E., Kalu, U.G., Filippini, N., Mackay, C.E., Ebmeier, K.P., 2011. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 32, 2322 e2325-2318.

Small, S.A., Duff, K., 2008. Linking Abeta and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. Neuron 60, 534-542.

Smith, E.E., Jonides, J., 1999. Storage and executive processes in the frontal lobes. Science 283, 1657-1661.

Song, S.K., Sun, S.W., Ju, W.K., Lin, S.J., Cross, A.H., Neufeld, A.H., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 20, 1714-1722.

Song, S.K., Sun, S.W., Ramsbottom, M.J., Chang, C., Russell, J., Cross, A.H., 2002. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 17, 1429-1436.

Song, S.K., Yoshino, J., Le, T.Q., Lin, S.J., Sun, S.W., Cross, A.H., Armstrong, R.C., 2005. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage 26, 132-140.

Spreng, R.N., Wojtowicz, M., Grady, C.L., 2010. Reliable differences in brain activity between young and old adults: a quantitative meta-analysis across multiple cognitive domains. Neurosci Biobehav Rev 34, 1178-1194.

Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu Rev Neurosci 27, 279-306.

Toepper, M., Gebhardt, H., Beblo, T., Thomas, C., Driessen, M., Bischoff, M., Blecker, C.R., Vaitl, D., Sammer, G., 2010. Functional correlates of distractor suppression during spatial working memory encoding. Neuroscience 165, 1244-1253.

Unsworth, N., Engle, R.W., 2007. The nature of individual differences in working memory capacity: active maintenance in primary memory and controlled search from secondary memory. Psychol Rev 114, 104-132.

Unsworth, N., Engle, R.W., 2007. On the division of short-term and working memory: an examination of simple and complex span and their relation to higher order abilities. Psychol Bull 133, 1038-1066.

Verhaeghen, P., Cerella, J., 2002. Aging, executive control, and attention: a review of meta-analyses. Neurosci Biobehav Rev 26, 849-857.

Vincent, G.K., Velkoff, V.A., 2010. The Next Four Decades, The Older Population in the United States: 2010 to 2050. Current Population Reports. U.S. Census Bureau, Washington, D.C.

Vos, S.B., Jones, D.K., Jeurissen, B., Viergever, M.A., Leemans, A., 2012. The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain. Neuroimage 59, 2208-2216.

Wager, T.D., Smith, E.E., 2003. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci 3, 255-274.

Wager, T.D., Smith, E.E., 2003. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci 3, 255-274.

Wang, C., Stebbins, G.T., Medina, D.A., Shah, R.C., Bammer, R., Moseley, M.E., deToledo-Morrell, L., 2012. Atrophy and dysfunction of parahippocampal white matter in mild Alzheimer's disease. Neurobiol Aging 33, 43-52.

Wechsler, 2001. Weschler Test of Adult Reading. The Psychological Corporation, San Antonio, TX.

Welsh, K., Butters, N., Hughes, J., Mohs, R., Heyman, A., 1991. Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. Arch Neurol 48, 278-281.

Welsh, K.A., Butters, N., Hughes, J.P., Mohs, R.C., Heyman, A., 1992. Detection and staging of dementia in Alzheimer's disease. Use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease. Arch Neurol 49, 448-452.

Wendelken, C., Bunge, S.A., Carter, C.S., 2008. Maintaining structured information: an investigation into functions of parietal and lateral prefrontal cortices. Neuropsychologia 46, 665-678.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Backman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., van Duijn, C., Visser, P., Petersen, R.C.,

2004. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256, 240-246.

Yaffe, K., Petersen, R.C., Lindquist, K., Kramer, J., Miller, B., 2006. Subtype of mild cognitive impairment and progression to dementia and death. Dement Geriatr Cogn Disord 22, 312-319.

Yakovlev, P.A., Lecours, I.R., 1967. The myelogenetic cycles of regional maturation of the brain. In: Minokowski, A. (Ed.), Regional development of the brain in early life. Blackwell, Oxford, pp. 3-70.

Yasmin, H., Nakata, Y., Aoki, S., Abe, O., Sato, N., Nemoto, K., Arima, K., Furuta, N., Uno, M., Hirai, S., Masutani, Y., Ohtomo, K., 2008. Diffusion abnormalities of the uncinate fasciculus in Alzheimer's disease: diffusion tensor tract-specific analysis using a new method to measure the core of the tract. Neuroradiology 50, 293-299.

Yetkin, F.Z., Rosenberg, R.N., Weiner, M.F., Purdy, P.D., Cullum, C.M., 2006. FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur Radiol 16, 193-206.

Zhuang, L., Wen, W., Zhu, W., Trollor, J., Kochan, N., Crawford, J., Reppermund, S., Brodaty, H., Sachdev, P., 2010. White matter integrity in mild cognitive impairment: a tract-based spatial statistics study. Neuroimage 53, 16-25.

CHAPTER 2

METHODS

Participants

In total, 52 older adults were recruited from the surrounding Athens area through newspaper advertisements and community engagement. Community interactions included giving “Brain Health” talks at various private and public organizations and centers, including assisted living facilities, caregiver support groups, and the Athens-Clarke county public library. Following these talks participants were informed of the details of the study and were given flyers with the appropriate contact information.

Of the 52 participants who were recruited for the study, 40 (24 controls, 16 MCI) were included in the current analyses; 6 participants were identified with AD and 6 participants were not able to complete the entire MR scanning protocol.

Inclusion Criteria

Before partaking in the study, participants underwent an initial phone screen. Inclusion criteria included compatibility with the MRI environment, between 65 – 85 years of age, confirmation of a reliable collateral, literate, and no history of a neurological disorder. Participants who enlisted in the study were screened once more upon arriving on the first day of testing. Upon completion all were given $100 for participation. Additionally, upon their or the collateral’s request a contact sheet with referral sources for a neuropsychological exam was provided.

Measures

Participants and collaterals were interviewed with the Clinical Dementia Rating (CDR) scale, a semi-structured interview designed to assess an individual's level of dementia-related impairment. The CDR obtains collateral-based information regarding the individual being assessed, in this case the participant, and also asks the collateral to recall and detail two recent events in order to test the participant's LTM. Information acquired from both parties is divided into six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Hughes et al., 1982). Each domain is scored individually on a five-point dementia impairment scale (i.e., 0.0 none, 0.5 questionable, 1.0 mild, 2.0 moderate, 3.0 severe), except personal care, which is scored on a four-point scale (i.e., 0.0 none, 1.0 mild, 2.0 moderate, 3.0 severe), using a set of criteria and clinical judgment. Scores are tallied based on an algorithm (Morris, 1993) to arrive at a Global CDR score. The global score is also assessed on the above five-point scale and indicates degree of dementia (Morris, 1997). The diagnosis of MCI has been supported by a CDR global score of 0.5 (Morris, 1993), but the use of this criteria has been debated as those with very mild dementia may be grouped into the same category. An alternative staging guideline which has been shown to have good sensitivity and specificity is to assess the sum of boxes (SB) scores of the CDR (O'Bryant et al. 2008; 2010). Using this guideline, those with a GS of 0.5 and SB scores of 0.5-2.0 are classified as questionable dementia or MCI, while those with a GS of 0.5 and SB scores of 2.5-4.0 are classified as very mild dementia. The MCI sample for the current study had a GS of 0.5 and an SB average of 1.16.

Participants were also administered several cognitive measures as part of a larger study, most of which were not specific to the current study. The RBANS (Randolph, 1998) was the only neuropsychological exam pertinent to the current analyses and is described below.

The RBANS is a comprehensive 30-minute battery designed for longitudinal assessment of an individual's neuropsychological status. It contains 12 subtests which generate 5 index scores and a total score. Indices include immediate memory, visuospatial/constructional, language, attention, delayed memory and total scale. Reliability and validity tests for the RBANS can be found in Randolph (1998), but will be described here. The RBANS was standardized on a sample of 540 adults, divided into six age groups: 20-39, 40-49, 50-59, 60-69, 70-79, and 80-89. Sex and race/ethnicity for each sample age group were proportionate to the levels indicated by the U.S. Census report of 1995; education level was broken up into three levels of education: less than high school, high school, and greater than high school. The average reliability coefficient for each index across age groups was: Total = .94, immediate memory = .88, visuospatial/constructional = .80, attention = .85, language = .82, and delayed memory = .83. Convergent and divergent construct validity of the RBANS was established based on patient groups. Comparisons between various well known neuropsychological measures demonstrated the RBANS correlated highly with most of these measures; correlations exhibiting low Pearson's r were likely due to the sample sizes used and some of the RBANS indices exhibiting higher sensitivity to impairment. The RBANS has shown high levels of sensitivity and specificity to AD (Duff et al., 2008), and has been reported to

have strong specificity but low sensitivity to MCI (Duff et al., 2010). This latter finding is not surprising being that MCI is such a heterogeneous syndrome.

Task and Stimuli

Participants performed three separate fMRI runs, each with a different active task (Fig. 2.1). In order of presentation they were: a visuo-spatial attention (VSA) task, a verbal STM task, and CWKMS task. The CWKMS task is the combination of the VSA and verbal STM tasks. Each run had the same active baseline to account for motor responses during the tasks. During each run only the right index finger was used to respond. During the baseline participants responded to the presentation of a right pointing arrow presented to the right of a fixation cross. The arrow was presented for 4.5 s with an inter-stimulus interval (ISI) of 2.25 s; the fixation cross remained on the screen during the ISI.

During the VSA task participants were presented with a fixation cross around which dots of different colors were randomly presented one at a time in any of the four cardinal orientations. The possible colors were red, green, yellow, and blue, and the object of the task was to manually respond when the dot was red. Dot trials were presented for 4.5 s, while the ISIs lasted for 2.25 s.

During the verbal STM task participants were presented with 4 letters, each for 2.25 s. Participants were asked to remember the letters in the presented order. During the letter ISI participants were presented with a right pointing arrow which they responded to with a button press, arrow presentation lasted for 4.5 s. Proceeding the letter presentation block, there was a letter array recognition block with four separate arrays; each array was presented for 3.75 s. Participants responded when they were presented with an array

displaying the previously remembered letters in the correct order. The correct array could have been presented more than once or not at all.

As previously stated, the CWKMS task consisted of a combination of the VSA and STM tasks. The presentation of each letter alternated with the presentation of the VSA task. Timing for the task was kept the same as the component tasks; each letter was presented for 2.25 s and the attention trials lasted 4.5 s. After the complex block participants were presented with letter arrays as in the STM and also responded to the correct letter sequence. A detailed presentation scheme is shown in figure 2.1. Note that a 3 s cue was presented before the baseline block and a 6 s cue was presented before the task and recall blocks. Tasks were designed in E-Prime v 2.0 (Psychology Software Tools, Pittsburgh, PA).

Imaging Procedure

Participants initially practiced each task by viewing them on a computer monitor and tapping their finger to the appropriate response as they would with the response pads in the MRI unit. Participants practiced the task until the investigator acknowledged they were performing the task appropriately. After practice, participants were placed in the MRI scanner. Participants initially underwent a 3D high resolution structural scan after which they then performed 1 run of each of the 3 tasks. Following completion of these tasks, participants underwent several other scans, including the DTI scan and phase map acquisition. The task was presented through MRI compatible goggles (Resonance Technology Inc., Northridge, CA.), participants responded through Cedrus Lumina LU400 MRI compatible response pads (Cedrus, San Pedro, CA.) by using their index and

middle fingers, and responses and reaction times (RTs) were recorded by E-Prime. Behavioral data was acquired during all 3 runs in the scanner.

MRI Acquisition

All scans were acquired using a General Electric (GE; Waukesha, WI) Signa HDx 3T MRI. 3D structural scans were acquired using a fast spoiled gradient recalled echo (FSPGR) protocol; TE = min full, TR = 7.5 ms, flip angle = 20°, 180 axial slices, slice thickness = 1 mm, and FOV = 256 x 256 mm. These images covered from the top of the head to the brainstem and acquisition took approximately 6 min 20 s. FMRI scans were acquired using a T2*-weighted single shot echo planar imaging (EPI) sequence and were aligned to the intercommisural line (AC-PC line); TE = 25 ms, TR = 1500 ms, 90° flip angle, 30 interleaved slices, acquisition matrix = 64x64, spacing = 0 mm, slice thickness = 4 mm, FOV = 240 x 240 mm, and ASSET factor = 2. Functional images covered the entire cortical surface and a portion of the cerebellum. The VSA run lasted for 5 min and 45 s, while the verbal STM and CWKMS runs lasted for 7 min and 15 s.

Diffusion weighted imaging (DWIs) scans were acquired using a single-shot diffusion-weighted SE-EPI sequence following the same orientation and anatomical coverage of the functional scans; TE = min full, TR = 15000 ms, 90° flip angle, 60 interleaved slices, slice gap = 0 mm, 2 mm isotropic voxels, acquisition matrix = 128 x 128, FOV = 256 x 256 mm, parallel acceleration factor = 2, b-value: 1000, and 30 optimized gradient directions with 3 b0 images. Total scan time for the DTI acquisition was 9 min and 38 s. In between fMRI and DTI acquisition two pairs of magnitude and phase images were acquired for fieldmap-based unwarping of fMRI and DW images; TE1 = 5.0 ms and TE2 = 7.2ms, TR = 750 ms, 60 slices, slice gap = 0 mm, 2mm

isotropic voxels, acquisition matrix = 128 x 128, and FOV = 256 x 256 mm. acquisition for each pair of images took 1 min 40 s. Including participant and scanner-prep time, and other functional scans the participants underwent, total scan time was approximately 1 h and 15 min.

Data Analysis

All fMRI and DTI data were processed using the FMRIB Software Library (FSL; Smith et al., 2004; Woolrich et al., 2009). Before MRI data sets could be analyzed they were converted from their native GE DICOM format to NIFTI format using the dcm2nii conversion tool (Rorden, 2007). After conversion, fieldmaps calculated to correct the inherent distortion in both the fMRI and DWIs. Fieldmaps were made by: 1) adjusting the values of the phase maps (phase map 1 & 2) to have a range of [-pi, pi], 2) unwrapping (adjusting the values such that they are continuous) the phase maps using FSL's PRELUDE algorithm (Jenkinson, 2003), 3) calculating the fieldmap by subtracting phase map 2 from phase map 1 and dividing by the difference in echo times, 4) and finally denoising the fieldmap using FUGUE algorithm (Jenkinson, 2003).

FMRI

FMRI pre-processing consisted of the following steps. Brain extracting the anatomical and functional images using the Brain Extraction Tool (BET; Smith, 2002); motion correction using the Motion Correction FMRIB Linear Registration Tool (MCFLIRT; Jenkinson et al., 2002); slice time correction; fieldmap correction; smoothing using a 6 mm isotropic FWHM Gaussian kernel; application of a high-pass temporal filter, calculated at 63 s for the VSA (duration of baseline and task blocks,

including cues) task and 81 s for the STM and CWKMS tasks (duration of baseline, task, and recall blocks, including cues); and prewhitening data to remove temporal auto-correlations.

In order to more accurately identify task-induced BOLD responses, each run's time course was convolved with a double-gamma hemodynamic response function in the first-level analyses. Additionally, head motion parameters estimated from MCFLIRT were added as regressors to each run to aid in removing signal artifacts due to motion. The contrast of interest for each run was task – baseline. For the verbal STM and CWKMS tasks the recall portion was also contrasted against baseline. Results were normalized to the standard MNI space 91x109x91 by warping them to the 3D anatomical and then applying low dimensional non-linear warp parameters calculated from non-linearly warping (mm warp resolution) the 3D anatomical to MNI space.

Within group contrasts were performed using a fixed effects model. Contrasts of interest included all three tasks minus each respective baseline, CWKMS – VSA, CWKMS and verbal STM recall – baseline, and CWKMS – verbal STM recall. Between group comparisons were performed using a mixed effects model and FLAME 1 + 2. Contrasts of interest included controls (CON) – MCI and MCI – CON for each task – baseline, CWKMS – VSA, CWKMS recall – baseline, verbal STM recall – baseline, and CWKMS recall – verbal STM recall. Cluster based thresholding was implemented for all fMRI statistical analyses.

DTI

DWI images were pre-processed by applying the FMRIB Diffusion Toolbox (FDT; Behrens et al., 2003) eddy current correction tool, motion corrected using the first b0 image as a reference, brain extracted using BET, and then distortion corrected using the calculated fieldmaps. Diffusion tensors were then estimated using DTIFIT.

To enhance the ability to detect diffusivity differences in MCI, Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) were employed. TBSS attempts to alleviate many of the problems associated with standard voxel-based approaches by initially optimizing registration of the FA images to standard MNI space. For this study, the subject most representative of the entire sample was identified by TBSS and used as an initial target image for the rest of the sample, this image was then affine registered to MNI space. The remaining FA images were then transformed to MNI space by combining the non-linear warp used to register them to the initial target image with the affine transformation of the target image to MNI space. TBSS further attempts to correct for subject mis-registration and consequent variability by producing a mean FA image and skeletonizing it. Each subject's FA data are skeletonized by projecting the nearest maximum FA values onto the skeleton.

Analyses of the skeletonized images were carried out using FSL's Randomise (Nichols and Holmes, 2002), which performs nonparametric, permutation based testing. In order to enhance detection of diffusivity differences between groups threshold-free cluster-enhancement (TFCE; enhanced for diffusion data) was employed. TFCE relies on neighborhood information, like cluster based thresholding, but is thought to be superior as an initial cluster threshold does not have to be set thereby minimizing the problem of

overlooking the true signal. For each instance of Randomise, 5,000 permutations were run. After the t-statistics are calculated at each voxel, the appropriate TFCE p-values are calculated for each voxel. Any significant differences were identified by voxels where $p<0.05$. For each group, DA, DR, and MD were separately correlated with each index score of the RBANS and the total score. Between group comparisons aimed to identify whether the RBANS indices were sensitive to unique MCI-related white matter degeneration. This was achieved by testing for the interaction effect between group and each index score.

Power Analysis

To determine the necessary sample size for this study, Z-scores from a WKM fMRI study comparing MCI and controls (Yetkin et al., 2006) were used as a basis for conversion to Cohen's d. Only Z-scores from ROIs pertinent to the hypotheses were examined. From these the lowest Z-score was taken, as this would provide the most conservative estimate of the sample size needed to realize significant differences in the ROIs. The right middle frontal gyrus, part of the DLPFC, exhibited the lowest Z-score, 2.63. This score was converted to a Pearson's *r* using the formula, $r = Z/(N)^{1/2}$. The resulting *r*, 0.637869, was converted to Cohen's *d* using the formula, $d = 2r/(1-r^2)^{1/2}$. This resulted in a *d* of 1.65649. Lastly, G*Power 3 (Faul et al., 2007) was used to calculate the appropriate sample sizes for the groups. Parameters for G*Power were: a-priori analysis, t-tests for independent means (two groups), one-tailed, $\alpha = 0.05$, and power $(1 - \beta) = 0.95$. The power analysis calculated that a sample size of 9 would be needed for each group.

References

Behrens, T.E., Woolrich, M.W., Jenkinson, M., Johansen-Berg, H., Nunes, R.G., Clare, S., Matthews, P.M., Brady, J.M., Smith, S.M., 2003. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med 50, 1077-1088.

Duff, K., Hobson, V.L., Beglinger, L.J., O'Bryant, S.E., 2010. Diagnostic accuracy of the RBANS in mild cognitive impairment: limitations on assessing milder impairments. Arch Clin Neuropsychol 25, 429-441.

Duff, K., Humphreys Clark, J., O'Bryant, S., Mold, J., Schiffer, R., Sutker, P., 2008. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. Archives of Clinical Neuropsychology 23, 603-612.

Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39, 175-191.

Hughes, C.P., Berg, L., Danziger, W.L., Coben, L.A., Martin, R.L., 1982. A new clinical scale for the staging of dementia. Br J Psychiatry 140, 566-572.

Jenkinson, M., 2003. A Fast, automated, N-dimensional phase-unwrapping algorithm. Magn Reson Med 49, 193-197.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825-841.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412-2414.

Morris, J.C., 1997. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 9 Suppl 1, 173-176; discussion 177-178.

Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15, 1-25.

O'Bryant, S.E., Lacritz, L.H., Hall, J., Waring, S.C., Chan, W., Khodr, Z.G., Massman, P.J., Hobson, V., Cullum, C.M., 2010. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 67, 746-749.

O'Bryant, S.E., Waring, S.C., Cullum, C.M., Hall, J., Lacritz, L., Massman, P.J., Lupo, P.J., Reisch, J.S., Doody, R., 2008. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol 65, 1091-1095.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum Brain Mapp 17, 143-155.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487-1505.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation

as FSL. Neuroimage 23 Suppl 1, S208-219.

Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. Neuroimage 45, S173-186.

Yetkin, F.Z., Rosenberg, R.N., Weiner, M.F., Purdy, P.D., Cullum, C.M., 2006. FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur Radiol 16, 193-206.

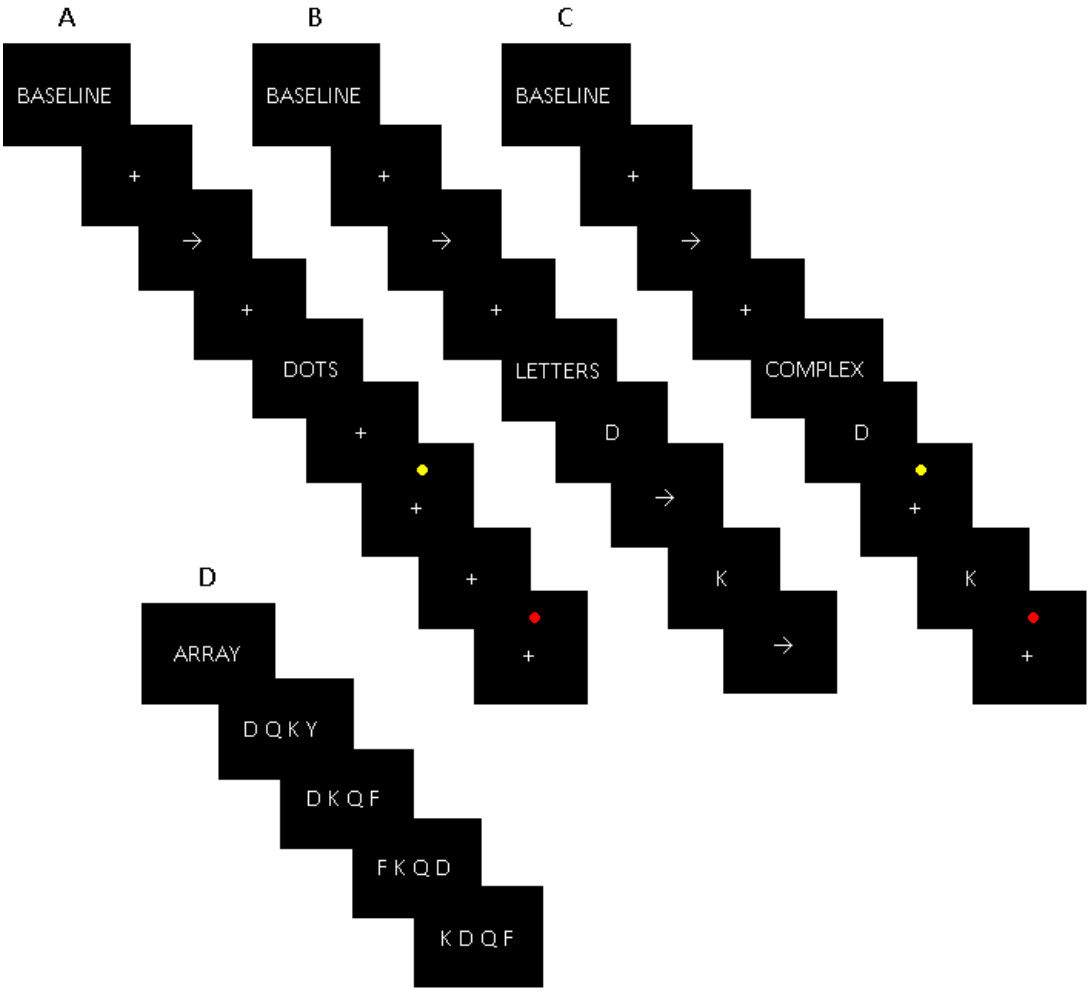

Figure 2.1. Depiction of distractor, verbal STM, and CWKMS task. For all tasks the baseline block is identical, participants are presented with a cue indicating the start of the baseline block and then have to press when they see the right-pointing arrow, A. Distractor task. Participants are cued to the start of the block by the word “DOTS” and then have to press when they see a red dot. B. Verbal STM. Participants are cued to the start of the block by the word “LETTERS.” They have to remember the letters presented (total of 4) in the order of presentation and must press when they see an arrow. C. CWKMS task. Participants are cued to the start of the block by the word “COMPLEX.” As in the previous trial they must remember the letters in order of presentation, but in between each letter presentation they must now attend to the presentation of a red dot. D. Array. Participants are cued to the start of the block by the word “ARRAY.” The array/retrieval condition follows both the verbal STM and CWKMS tasks. Participants must identify which of the arrays accurately represents the order of presentation of the letters. Please refer to the Task and stimuli section in the methods for further details.

CHAPTER 3

SUPERIOR TEMPORAL GYRUS HYPER-ACTIVATION AS A NOVEL BIOMARKER OF MILD COGNITIVE IMPAIRMENT[1]

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Abstract

Memory dysfunction in mild cognitive impairment (MCI) is primarily associated with episodic memory deficits linked to deterioration of the medial temporal lobes (MTLs). Current suggested criteria for the diagnosis of MCI call for the discovery of novel biomarkers. Functional activation differences in MCI during memory-task performance are often evidenced in the MTLs, and frontal and parietal lobes, but it has been suggested that examination of working memory (WKM) differences may be more useful in detecting MCI. In the current study, MCI and control participants performed a complex WKM span (CWKMS) task while functional magnetic resonance imaging (fMRI) data was acquired. Results indicated hyper-activation of the superior temporal gyrus (STG), MTLs, and the insula during encoding and maintenance, and hyperactivation of the STG, MTLs, insula, and ventromedial frontal and anterior cingulated cortices during recall for the MCI participants. MTL differences are consistent with previous findings, but such localized differences in the STG are quite novel. Hyper-activation of the STG during WKM encoding and maintenance suggests that long-term phonological mechanisms associated with regions of the STG are necessary to maintain items in the focus attention. Increased recruitment of these mechanisms for the MCI patients suggests that may be attempting to compensate for poor encoding abilities that may partly resulted from MTL neurodegeneration. Therefore, hyper-activation of the STG during WKM encoding and maintenance, and/or recall is a possible novel biomarker of MCI.

Introduction

In the aging population significant declines in cognitive abilities often result from dementing processes, of which the most common is Alzheimer's disease (AD). Of the 13.9% of individuals over the age of 70 undergoing a dementing process, AD has been estimated to account for nearly 70% of cases (Plassman et al., 2007). Preceding the period of readily observable and increasing deficits seen in dementia is a period of modest, but observable clinical impairment often termed mild cognitive impairment (MCI). Clinic-based estimates indicate 10-15% of those with a primary memory deficit, known as amnestic MCI (a-MCI), convert to AD annually (Roach, 2005), while population based estimates report conversion rates of 5-10% (DeCarli, 2003; Panza et al., 2005).

As with AD, memory impairments in MCI are mainly attributed to deterioration of the medial temporal lobes (MTLs), a region clearly associated with long term memory formation and consolidation (Milner, 1972; Squire et al., 2004). Structural magnetic resonance imaging (MRI) studies have revealed increased MTL atrophy in MCI compared to healthy controls (Colliot et al., 2008; Du et al., 2001; Killiany et al., 2002; Wolf et al., 2001), especially in those who later convert to neurodegenerative forms of dementia such as AD (Meyer et al., 2005). Diffusion imaging studies have found decreased fractional anisotropy and increased mean diffusivity in the hippocampus (Fellgiebel et al., 2004; Kantarci et al., 2009; Zhuang et al., 2010), both indicative of compromised structural integrity. Accordingly, many memory-based functional MRI (fMRI) studies of MCI typically find increased blood oxygen level-dependent (BOLD) responses in the MTLs (e.g., Celone et al., 2006; Dickerson et al., 2005; Johnson et al.,

2006; Miller et al., 2008; Yetkin et al., 2006). The MTLs are not the only regions in which activation differences are found; differences are also often found in frontal and parietal regions (e.g., Machulda et al., 2003; Yetkin et al., 2006). Thus, the current research criteria for MCI emphasize the discovery of reliable biomarkers, especially imaging based biomarkers indicative of neuronal injury, which may allow for the pre-clinical diagnosis of AD (Albert et al., 2011).

While many memory studies of MCI have focused on episodic memory impairment, it has been suggested that examination of working memory (WKM) related changes may be more useful in detecting MCI (Gagnon and Belleville, 2011). WKM is defined as a capacity-limited system which is integral to the maintenance and manipulation of items in the focus of attention and to the storage and retrieval of items in long term memory (LTM; Baddeley & Hitch, 1974; Broadbent, 1958; Cowan, 2005; McElree, 2006; Unsworth & Engle, 2007a). The WKM system is also crucial in maintaining information in the focus when attentional control is necessary to override automatic responses (Unsworth & Engle, 2007b). This indicates the WKM system is closely intertwined with aspects of executive functioning; specifically, WKM capacity, or the ability to maintain information in the focus of attention and exchange information between the focus and LTM, is limited by the individual's level of attentional control (Cowan 2005; Unsworth & Engle, 2007b). The aim of the present study was to examine WKM related BOLD signal differences in MCI to determine whether they may be useful biomarkers for the detection of MCI.

Working memory in mild cognitive impairment

Even though WKM impairments in AD are readily observed and have been well documented (e.g., Baddeley at al., 1986; Baddeley et al., 1991), relatively few studies have directly investigated WKM functioning in those with MCI (Alescio-Lautier et al., 2007; Belleville et al., 2007; Belleville et al., 2008; Brandt et al., 2009; Kessels et al., 2010; Saunders & Summers, 2011). Findings do indicate significant impairments in attention, executive functioning, and both verbal and visual WKM in MCI. For example, Belleville et al. (2007) observed MCI patients were impaired on verbal recall during both a dual task and when no interference was presented, indicating difficulty in maintaining items in the focus of attention. Similarly, Alescio-Lautier et al. (2007) reported that MCI patients were significantly impaired on visual and visuospatial WKM after a 30s delay with or without a distractor task presented before the probe image. Brandt et al. (2009) found that all MCI subtypes exhibited WKM and planning/problem solving deficits. Kessels et al. (2010) reported deficits in bound information (e.g., object-location) in MCI patients, especially for high-load conditions. Lastly, Saunders and Summers (2011) reported deficits in a-MCI and non-amnestic MCI across a number of domains including attention, spatial WKM, and visuospatial span.

One type of WKM task that may be useful in distinguishing MCI-to-AD converters from non-converters are the complex WKM span (CWKMS) tasks. CWKMS tasks require the concurrent processing of irrelevant and to-be-remembered information, and therefore, a high degree of executive attentional control (Conway et al., 2003; Engle et al., 1999; Kane et al., 2004; Kane et al., 2007). Given that the to-be remembered information is properly encoded, it may be placed into LTM to accommodate the

processing of irrelevant information and may then be retrieved as necessary (Kane et al., 2007). The process of retrieval from LTM is performed through a controlled search for the appropriate items (Unsworth & Engle, 2007b). The high degree of executive attentional-control and access to LTM required to perform CWKMS tasks make them valuable tools to assess those with MCI, as they have been shown to display deficits in both domains.

To date, only one study has utilized CWKMS tasks to examine WKM in persons with MCI. Gagnon and Belleville (2011) found that by varying the retention interval they could differentiate MCI-to-AD converters from non-converters, information not gleamed from the other neuropsychological measures which were administered. CWKMS tasks have also proven to be sensitive to WKM impairment in healthy individuals carrying the apolipoprotein ε4 allele, a genetic risk factor for AD, while simple span tasks were not (Rosen et al., 2002). Additionally, CWKMS tasks are more sensitive to verbal memory span deficits in healthy, older adults than simple span tasks (Bopp & Verhaghen, 2005).

Functional neuroimaging of working memory in mild cognitive impairment

While functional imaging studies of WKM in MCI are extremely limited, there have been studies of related cognitive processes in MCI. In general, neuroimaging studies of memory comparing MCI patients to healthy controls or those with AD often detect activation differences in frontal, parietal, and MTL regions. (e.g., Bokde et al., 2010; Hampstead et al., 2011; Kircher et al., 2007; Kochan et al., 2010; Kochan et al., 2011; Machulda et al., 2003; Yetkin et al., 2006). Likely due to the various paradigms used across studies and the heterogeneous nature of and performance differences seen in MCI,

the direction of activation differences are not necessarily consistent. For example, in one of the earliest fMRI memory studies on MCI patients, Machulda et al. (2003) found that during encoding of a visual scene, MCI and AD subjects displayed reduced MTL activation as compared to controls. Hampstead et al. (2011) also detected reduced MTL activity during encoding and storage. Conversely, using a visual WKM paradigm, Yetkin et al. (2006) found that MCI subjects exhibited greater right parahippocampal gyrus activation than AD patients and controls, while AD patients exhibited greater left parahippocampal gyrus activity than both MCI subjects and controls. Kircher et al. (2007) demonstrated that successful encoding in MCI is associated with increased hippocampal activation compared to controls. In a longitudinal study, Miller et al. (2008) found that increased hippocampal activity during memory tasks is predictive of incipient cognitive decline and suggest its use as a biomarker of MCI. This fits well with the idea that MCI patients are engaging compensatory mechanisms in order to attempt to maintain a pre-morbid level of functioning. In other words, because AD pathology is thought to initially have its most notable effects on the MTLs, increased activity in this region during initial neurodegeneration (during MCI) is thought to help maintain pre-morbid functioning.

Kochan and colleagues (2010; 2011), however, have suggested the use of load-varied functional activation patterns in regions other than the MTLs as a biomarker for MCI. Kochan et al. (2010) indicated that community dwelling MCI subjects show increased activation in the anterior cingulate cortex (ACC) and precuneus during encoding of lower load conditions as compared to healthy older adults. During the high load condition MCI subjects displayed decreased activation in these regions during

encoding and demonstrated a greater degree of hypoactivation in a posterior cingulate / medial precuneus region. Kochan et al. (2011) further demonstrated that greater load induced deactivation in the posteromedial cortex (medial precuneus, posterior cingulate, and retrosplenial cortex) significantly predicted functional decline in activities of daily living for MCI subjects over a 2-year period.

Similar effects of load are seen in activation pattern differences between two separate studies. In a verbal delayed match to sample task (Bokde et al., 2010), where participants were asked to remember 5 letters, a-MCI patients displayed greater frontal, temporal, and inferior parietal activation during encoding and maintenance compared to their performance matched controls. When subjects were asked to remember 5 object-location associations, a much higher load, an overall reduction of brain activity in MCI subjects was detected during encoding (Hampstead et al., 2011). Furthermore, it was shown that regions activated across various phases of the task were much more similar for the MCI group than controls. The authors suggest that along with the fact those with MCI did not recruit dorsolateral prefrontal cortex (DLPFC) throughout the task, these findings further support the idea that impaired WKM functioning in MCI may result from impaired executive abilities.

Current study

As previously stated, CWKMS tasks have been shown to be more sensitive to cognitive deficits than simple span tasks in healthy older adults (Bopp & Verhaghen, 2005), sensitive to deficits in apolipoprotein ε4 carriers (Rosen et al., 2002), and prognostic of conversion to AD in an MCI sample not differentiable by other measures

(Gagnon & Belleville, 2011). The goal of the current study was to examine whether functional activation in MCI patients in response to a CWKMS task would provide novel insight regarding the emergence of cognitive deficits in MCI. This is the first study that we are aware of to use CWKMS tasks while acquiring BOLD data from those with MCI.

CWKMS tasks consist of an encoding and maintenance phase, and a separate recall phase. Therefore, BOLD signal differences were examined during each of these phases, with the encoding and maintenance phase being of most interest; it has been established that MCI and AD patients display deficits in recall, but there is evidence that the primary memory deficit in AD may be one of encoding (Germano & Kinsella, 2005; White & Ruske, 2002). Previous neuroimaging studies using CWKMS tasks have shown that CWKMS encoding and maintenance requires the recruitment of the DLPFC, ventrolateral prefrontal cortex (VLPFC), ACC, inferior parietal lobule (IPL), superior parietal lobule (SPL), precuneus, hippocampus, and even the insula (Chein et al., 2010, Faraco et al., 2011; Kondo et al., 2004). Recall, or controlled retrieval, of information has been shown to elicit greater activation in the MTL and PFC as compared to a storage only or STM condition. We expected that if groups performed equally, the MCI group would exhibit greater activation during encoding and maintenance in the frontal and medial temporal lobes. This hypothesis is based on the well-known fact that MCI patients show deficits in LTM functioning (Albert et al., 2011; Petersen et al., 2001), often associated with the MTLs, and have been shown to display significant executive deficits (Belleville et al., 2007; Brandt et al., 2009; Saunders & Summers, 2011), often associated with frontal regions. Increased activation would be consistent with compensatory views of functional activation and evidence that MCI patients exhibit WKM-related differences

across many of these regions. Following Kochan et al. (2010), who had MCI patients perform a graded WKM challenge, we expected that participants with MCI would also exhibit reduced PPC activation in comparison to healthy older adults due to the high load induced by the CWKMS task. Since the goal of the current study was to find novel biomarkers of MCI by implementing a CWKMS task, we also expected to find functional activation differences in regions not typically associated with MCI dysfunction. Lastly, we also hypothesized that the MCI group would exhibit significantly greater activation in the MTLs and PFC during CWKMS recall.

Methods

Participants

In total, 52 older adults were recruited from the local community through newspaper advertisements and community engagement. Community interactions included giving "Brain Health" talks at various private and public organizations and centers, including assisted living facilities, caregiver support groups, and the local public library. Following these talks participants were informed of the details of the study and were given flyers with the appropriate contact information.

Of the 52 participants that were recruited for the study, 40 (24 controls, 16 MCI) were included in the current analyses; 6 participants were identified with AD and 6 participants were not able to complete the entire MR scanning protocol.

Inclusion criteria

Before partaking in the study, participants underwent an initial phone screen. Inclusion criteria included compatibility with the MRI environment, between 65 – 85 years of age, confirmation of a reliable collateral, literate, and no self-reported history of a neurological disorder. Participants who enlisted in the study were screened once more upon arriving on the first day of testing. Upon completion all were given $100 for participation. Additionally, upon their or the collateral's request a contact sheet with referral sources for a clinical cognitive assessment was provided.

Measures

Participants and collaterals were interviewed with the Clinical Dementia Rating (CDR) scale, a semi-structured interview designed to assess an individual's level of dementia-related impairment. The CDR obtains collateral-based information regarding the individual being assessed, in this case the participant, and also asks the collateral to recall and detail two recent events in order to test the participant's LTM. Information acquired from both parties is divided into six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Hughes et al., 1982). Each domain is scored individually on a five-point impairment scale (i.e., 0.0 none, 0.5 questionable, 1.0 mild, 2.0 moderate, 3.0 severe), except personal care, which is scored on a four-point scale (i.e., 0.0 none, 1.0 mild, 2.0 moderate, 3.0 severe), using a set of criteria and clinical judgment. Scores are tallied based on an algorithm (Morris, 1993) to arrive at a Global CDR score. The global score is also assessed on the above

five-point scale and indicates degree of dementia (Morris, 1997). The diagnosis of MCI has been supported by a CDR global score of 0.5 (Morris, 1993).

Task and stimuli

Participants performed three separate runs, each with a different active task (Fig. 3.1). In order of presentation they were: a visuo-spatial attention (VSA) task, a verbal STM task, and CWKMS task. The CWKMS task was a combination of the VSA and verbal STM tasks. Each run had the same active baseline to account for motor responses during the tasks. During each run only the right index finger was used to respond. During the baseline blocks of each run participants responded to the presentation of a right pointing arrow presented to the right of a fixation cross. The arrow was presented for 4.5 s with an inter-stimulus interval (ISI) of 2.25 s; the fixation cross remained on the screen during the ISI.

During the VSA task participants were presented with a fixation cross around which dots of different colors were randomly presented one at a time in any of the four cardinal orientations; the possible colors were red, green, yellow, and blue. The object of the task was to manually respond when the dot was red. Dot trials were presented for 4.5 s, while the ISIs lasted for 2.25 s. During the verbal STM task participants were presented with 4 letters, each for 2.25 s. Participants were asked to remember the letters in the presented order. During the letter ISI participants were presented with a right pointing arrow which they responded to with a button press, arrow presentation lasted for 4.5 s. Proceeding the letter presentation block, there was a letter recognition block with four separate arrays; each array was presented for 3.75s. Participants responded when they

were presented with an array displaying the previously remembered letters in the correct order. The correct array could have been presented one or more times, or not at all. As previously stated, the CWKMS task consisted of a combination of the attention and STM tasks. The presentation of each letter alternated with the presentation of the attention task. Timing for the task was kept the same as the component tasks; each letter was presented for 2.25 s and the attention trials lasted 4.5 s. After the complex block participants were presented with letter arrays as in the STM and also responded to the correct letter sequence. Note that a 3 s cue was presented before the baseline block and a 6 s cue was presented before the task and recall blocks.. Tasks were designed in E-Prime v 2.0 (Psychology Software Tools, Pittsburgh, PA).

Imaging procedure

Participants initially practiced each task by viewing them on a computer monitor outside the scanner and tapping their finger to the appropriate response as they would with the response pads in the MRI unit. Participants practiced the task until the investigator verified they performed the three recall blocks in the practice run correctly; participants indicated one correct array in the first block, none in the second block, and two in the third block. After practice, participants were placed in the MRI scanner. Participants initially underwent a 3D high resolution structural scan after which they then performed 1 run of each of the 3 tasks. Task were presented through MRI compatible goggles (Resonance Technology Inc., Northridge, CA.), participants responded through Cedrus Lumina LU400 MRI compatible response pads (Cedrus, San Pedro, CA.) by using their right index finger, and responses and reaction times (RTs) were recorded by

E-Prime. Behavioral data were acquired during all 3 runs in the scanner.

MRI acquisition

All scans were acquired using a General Electric (GE; Waukesha, WI) 3T Signa HDx MRI system. 3D structural scans were acquired using a fast spoiled gradient recalled echo (FSPGR) protocol; TE = min full, TR = 7.5 ms, flip angle = 20°, 180 axial slices, slice thickness = 1 mm, and FOV = 256 x 256 mm. These images covered from the top of the head to the brainstem and acquisition took approximately 6:20. FMRI scans were acquired using a T2*-weighted single shot echo planar imaging (EPI) sequence and were aligned to the intercommisural line (AC-PC line); TE = 25 ms, TR = 1500 ms, 90° RF pulse, 30 interleaved slices, acquisition matrix = 64x64, spacing = 0 mm, slice thickness = 4 mm, FOV = 240 x 240 mm, and ASSET factor = 2. Functional images covered the entire cortical surface and a portion of the cerebellum. The attention run lasted for 5 min and 45 s and consisted of 230 volumes, while the verbal STM and CWKMS runs lasted for 7 min and 15 s and consisted of 290 volumes. Two pairs of magnitude and phase images were acquired for fieldmap-based unwarping of the fMRI images; acquisition for each pair of images took 1 min and 40 s.

Data analysis

All fMRI data were processed using the FMRIB Software Library (FSL; Smith et al., 2004; Woolrich et al., 2009). Before analyses, data were converted from their native GE DICOM format to NIFTI format using the dcm2nii conversion tool (Rorden, 2007). After conversion, fieldmaps were produced to correct for the inherent distortion of the

echo planar images. Fieldmaps were calculated using FSL's PRELUDE and FUGUE (Jenkinson, 2003) programs.

FMRI pre-processing consisted of the following steps. Brain extracting the anatomical and functional images using the Brain Extraction Tool (BET; Smith, 2002); motion correction using the Motion Correction FMRIB Linear Registration Tool (MCFLIRT; Jenkinson et al., 2002); slice time correction; fieldmap correction; smoothing using a 6 mm isotropic FWHM Gaussian kernel; application of a high-pass temporal filter, calculated at 63 s for the VSA (duration of baseline and task blocks, including cues) task and 81 s for the STM and CWKMS tasks (duration of baseline, task, and recall blocks, including cues); and prewhitening data to remove temporal auto-correlations, and prewhitening data to remove temporal auto-correlations.

In order to more accurately identify task-induced BOLD responses, each run's time course was convolved with a double-gamma hemodynamic response function in the first-level analyses. Additionally, head motion parameters estimated from MCFLIRT were added as regressors to each run to aid in removing signal artifacts due to motion. The contrast of interest for each run was task minus baseline. For the verbal STM and CWKMS tasks the recall portion was also contrasted against baseline. Results were normalized to the standard MNI space 91x109x91 by warping them to the 3D anatomical and then applying low dimensional non-linear warp parameters calculated from non-linearly warping (mm warp resolution) the 3D anatomical to MNI space.

Within group contrasts were performed using a fixed effects model. Contrasts of interest included all three tasks minus each respective baseline, CWKMS – VSA, CWKMS and verbal STM recall – baseline, and CWKMS – verbal STM recall. Between

group comparisons were performed using a mixed effects model and FLAME 1 + 2 which carries out a Markov Chain Monte Carlo sampling to implicitly estimate the mixed effects variance. Contrasts of interest included controls (CON) – MCI and MCI – CON for each task – baseline, CWKMS – VSA, CWKMS recall – baseline, verbal STM recall – baseline, and CWKMS recall – verbal STM recall. Cluster based thresholding was implemented for all fMRI statistical analyses.

Results

Sample characteristics and behavioral responses

Groups did not significantly differ on age (t=0.5, p=0.6), but significantly differed on years of education (t=3.028, p=0.0044). Statistics for the behavioral data collected during the fMRI tasks are listed in Table 3.1.

Within group paired t-tests demonstrated that both groups had quicker RTs in response to the red dot during the VSA task than the CWKMS task (CON: $t = 5.431$, $p < 0.001$; MCI: $t = 5.030$, $p < 0.001$). Paired t-tests also demonstrated that the MCI group had significantly quicker RTs to the correct arrays during the CWKMS task than the verbal STM task ($t = 3.021$; $p = 0.009$). Paired t-tests did not show a significant difference in the number of correct array responses during the CWKMS task as compared to the verbal STM task. Between groups, independent sample t-tests showed significantly greater correct recall responses for the control group during verbal STM recall ($t = 2.134$, $p = 0.039$), but not during CWKMS recall. Significantly quicker RT were also evidenced for the control group during verbal STM recall ($t = 2.409$, $p = .021$), but not during CWKMS recall.

Within group whole brain analyses

Within group contrasts were performed for both CON and MCI for each of the three tasks compared to baseline (Fig. 3.2). For the CWKMS task both groups displayed significant levels ($Z > 4.5$, $p = .05$) of widespread bilateral activation in regions typically associated with WKM functioning, including DLPFC, VLPFC, cingulate cortex, IPL, SPL, precuneus, and the parahippocampal gyrus / hippocampus. Overall activation ($Z > 4.5$, $p = .05$) during the verbal STM was much less dispersed than for CWKMS for both groups, however, bilateral activation still overlapped with regions involved in CWKMS. Areas of activation included DLPFC, VLPFC, and IPL. For both the CWKMS and verbal STM tasks, activation appeared to be more dispersed for the MCI group. Clusters of activation for the VSA task ($Z > 4.5$, $p = .05$) differed across the two groups. Regions of activation for the CON group included the occipital pole, lingual gyrus, precuneus, middle temporal gyrus, superior temporal gyrus, Heschl's gyrus, precuneus, posterior cingulate, DLPFC, ACC, and superior frontal gyrus. Activation for the MCI group was seen in the occipital pole, lingual gyrus, DLPFC, middle temporal gyrus, ACC, and superior frontal gyrus.

Between group working memory analyses

Between group comparisons for the CWKMS, verbal STM, and VSA tasks did not yield any significant differences at the standard $Z > 2.3$, $p = .05$, for cluster-based thresholding. Lowering the threshold to $Z > 2.0$, $p = .05$, yielded significant differences for MCI – CON on the encoding and maintenance blocks of the CWKMS task (Fig. 3.3). Notably, the cluster encompassed areas of the left hippocampus, amygdala, and insula

(Table 3.2). Significant differences were also evidenced for the MCI – CON, CWKMS – VSA contrast ($Z > 2.3$, $p = .05$), a contrast designed to reveal unique differences in the ability to maintain information in the focus of attention (Fig. 3.3). Notably, one cluster encompassed areas of the left superior temporal gyrus (STG; Heschl's gyrus and planum temporale) and parietal and central operculum; the second cluster, similar to the cluster in the previous CWKMS contrast, encompassed portions of the left parahippocampal gyrus, hippocampus, amygdala, and insula (Table 3.3). Overall, results supported the hypothesis that the MCI group would significantly exhibit higher levels of activation in medial temporal regions. Results also showed significant activation differences in additional lateral temporal regions not hypothesized.

Between group recall analyses

Significantly higher levels of activation ($Z > 2.3$, $p = .05$) were evidenced for the MCI group for both the CWKMS and verbal STM recall blocks. For CWKMS recall (Fig. 3.4), the MCI group exhibited bilateral BOLD signal increases in many of the same regions as during maintenance and encoding; these included the insula, STG, and hippocampus. Additionally, several other significant differences were seen in the post-central and pre-central gyri, and ventromedial frontal and anterior cingulate cortex (Table 3.4). Significant differences during verbal STM recall were less pronounced (Fig. 3.4). One cluster was identified which encompassed the right temporal occipital fusiform cortex, middle temporal gyrus, lingual gyrus, and hippocampus (Table 3.5). The CWKMS recall – verbal STM recall contrast did not yield any significant differences in

either direction, indicating a similar linear increase in resource recruitment from verbal STM recall to CWKMS recall for both groups.

Discussion

Mild cognitive impairment (MCI) has been conceptualized as a "middle ground" between normal, healthy aging and dementia, usually of the Alzheimer's type. It is a heterogeneous syndrome, of which the most readily observable deficit is often that of poor episodic memory functioning (Albert et al., 2011; Petersen et al., 2001; Petersen & Bennett, 2005). Recent studies which have focused on discovering the full extent of cognitive impairments in MCI, have noted that MCI patients often display significant deficits in WKM and executive functioning and that these deficits may arise before those of episodic memory (Grober et al., 2008; Rapp & Reischies, 2005). Here we chose to use a complex working memory span (CWKMS) task to explore WKM differences between healthy older adults and those with MCI. A CWKMS task was chosen because CWKMS tasks have been shown to be ecologically valid and more effective than simple span tasks in detecting deficits in healthy older adults (Bopp & Verhaghen, 2005). Furthermore, they have been shown to differentiate MCI-to-AD converters from non-converters when other cognitive measures were not able to (Gagnon & Belleville, 2011). To our knowledge, this is the first study to examine WKM related functional activation differences between healthy older adults and MCI using a CWKMS task.

Within group differences

Within group analyses were performed to verify that groups were recruiting similar regions and that those were regions typically associated with the task. CWKMS task activation appeared to be consistent with areas typically recruited during performance of CWKMS (Chein et al., 2011; Faraco et al., 2011; Kondo et al., 2004) and other WKM tasks (Blumenfeld & Ranganath, 2006; Bunge et al., 2001; Chein & Feiz, 2001; Curtis & D'Esposito, 2003; D'Esposito & Postle, 1999; Postle et al., 2003), with the MCI group having more dispersed activation; this included activation in DLPFC, VLPFC, IPL, SPL, and MTL regions (Fig. 3.2). Dispersed activation during CWKMS for the MCI group is consistent with compensatory theories of functional activation in impaired populations, such that increased recruitment of ROIs are necessary to maintain normal task performance. Verbal STM task activation appeared to be reduced for both groups as compared to the CWKMS task, but activation was still evidenced in some WKM related regions such as the DLPFC and the IPL (Fig 3.2). Activation for the MCI group displayed greater bilateral intensity than that of the healthy older adult group. This is somewhat akin to the hemispheric asymmetry reduction in older adults (HAROLD) model that proposes that increased age, associated with decreased cognitive abilities, results in increasingly bilateral recruitment of task relevant regions (Cabeza, 2002). In other words, as task difficulty increases older adults rely more heavily on interhemespheric cooperation for successful task performance. Analyses of the VSA task demonstrated that the healthy older adult group appeared to show more dispersed and bilateral activation across occipital cortex, dorsomedial prefrontal cortex, and middle

temporal cortex (Fig. 3.2), regions typically associated with VSA. The reason for this reversal is not clear, but may be indicative of attentional deficits in MCI.

Between group working memory differences

As hypothesized, the MCI group exhibited significantly greater activation during performance of the CWKMS task in a cluster that encompassed portions of the left hippocampus, amygdala, and insula. These differences are consistent with previous studies demonstrating altered MTL activation in MCI compared to controls during WKM performance (Bokde et al., 2010; Machulda et al., 2003; Yetkin et al., 2006). Based on a number of studies demonstrating that those with MCI actually exhibit significant executive deficits, it was also hypothesized that the MCI group would recruit neo-cortical WKM related regions such as DLPFC and VLPFC to a greater extent than the healthy older adults, but such findings were not evidenced. Similarly, non-significant differences were evidenced for activation during the verbal STM task which also requires the recruitment of executive attentional and maintenance processes for proper task performance.

Because CWKMS tasks arise out of the combination of two distinct tasks, a distractor task and a memory task, contrasts of the CWKMS and distractor task may be used to shed light on memory specific processes (Chein et al., 2010; Faraco et al., 2011; Kondo et al., 2004). The two contrasts designed to shed light on the cognitive differences in WKM performance between MCI and healthy older adults were the MCI – CON and CON – MCI contrasts for CWKMS – VSA. Specifically, these contrasts aimed to reveal activation differences related to the encoding and active maintenance of to-be-

remembered information during WKM performance. If activation differences were mainly evidenced in medial temporal regions this would further support the idea that the main impairment in MCI is one of long term memory binding and storage, while if differences were also seen in frontal and parietal regions this would support the cognitive data indicating that MCI patients also experience significant executive deficits. The control group did not exhibit significantly higher levels of activation in any regions. Significantly higher levels of activation for the MCI group were evidenced along the left hippocampus, amygdala, and insula. Surprisingly, significant activation differences were also found along auditory and language cortical regions of the STG, such as Heschl's gyrus and the planum temporale.

MCI patients exhibited significantly higher levels of hippocampal activation under contrasts of overall CWKMS performance and a contrast aimed at revealing encoding and maintenance differences during CWKMS performance, supporting the idea that hippocampal dysfunction may be the main factor resulting in impaired memory performance in MCI. The hippocampus, though, consists of several subregions: the CA subfields, the subiculum, and the dentate gyrus (Amaral & Witter, 1989); the hippocampal formation includes the sub-regions just mentioned plus the entorhinal cortex (EC: Insausti, 1993). Histological research on dysfunction of the hippocampal formation in AD has shown that the EC is most vulnerable to AD neurodegeneration, while the CA1 region and subiculum of the hippocampus are also greatly affected (Braak et al., 2006; Gomez-Isla et al., 1996; Small et al., 2011; West et al., 1994). The EC, located in the anterior portion of the parahippocampal cortex, is the input gateway from the neocortex to the hippocampus, while the subiculum and CA1 output to the EC but can also

communicate with other subcortical and cortical regions, including the amygdala, medial and orbitofrontal cortices, and the anterior and posterior cingulate cortices. Functional activation differences in this study appeared to be localized around a cluster encompassing an area consistent with the location of the subiculum and CA1. Consistent with the current study, Fouquet et al. (2011) recently reported that CA1 volume was positively correlated with encoding performance in MCI. Even though significant differences were not evidenced around regions consistent with the location of the EC, which is most vulnerable to AD neurodegeneration, this does not indicate that compensatory mechanisms are not at work in the EC. Due to its ventral location it is difficult to obtain good signal-to-noise ratio in the EC, unlike the subiculum and CA1 which are situated dorsal to the EC.

An unexpected and quite interesting finding in this study was that of significant increases in activation in the left STG for the MCI group during CWKMS encoding and maintenance (Fig. 3.3). Specifically, STG differences were evidenced in the planum temporale, which forms part of Wernicke's area, and Heschl's gyrus. These regions are responsible for language comprehension and the perception of auditory stimuli, respectively, and are not typically thought of as WKM regions. Some studies, though, have shown that MCI, especially AD-converters, and AD patients show significant functional WKM activation differences (Bokde et al., 2010; Yetkin et al., 2006) and volumetric reductions in the STG (e.g., Bozzali et al., 2006; Fjell et al., 2009; Karas et al., 2008), among many other regions. In the current study, MCI hyper-activation of the STG was one of the few, localized differences evidenced between groups, and presents considerable implications in regards to our understanding of WKM system functioning .

From a cognitive perspective, these findings argue against some popular views on the neuroanatomical basis of WKM. For example, Baddeley's influential multi-component model of WKM suggests that verbal items are maintained in attention through direct access to a specialized verbal memory store, otherwise known as the phonological store/loop (Baddeley & Hitch, 1974; Gathercole & Baddeley, 1993). The neural mechanism supporting the phonological store has been equated with the IPL. Maintenance of verbally coded information in this phonological store is thought to be independent of any long-term linguistic representations. This is problematic because IPL activation is not evidenced during presentation of verbal information thought to interfere with the phonological loop (Buchsbaum & D'Esposito, 2008; Chein & Feiz, 2001; for an excellent formulation of this problem please see Acheson et al., 2011). Alternative models of WKM functioning propose that the focus of attention, also associated with parietal regions, is not domain specific and that WKM functioning is highly intertwined with LTM processes (e.g., Cowan, 2005; Oberauer, 2002; Unsworth & Engle, 2007a).

A few recent studies have aimed at identifying whether there are WKM storage-specific brain regions. Ravizza et al. (2011) found that subjects activated the STG during verbal, but not object, encoding and maintenance; they concluded that STG aids in maintaining phonological representations in an active state through a rehearsal or attentional refresh mechanism. Similarly, Acheson et al. (2011) used fMRI to map voxels in the posterior STG (ROI) and medial temporal gyrus (control region) involved in the phonological and lexical-semantic retrieval of words, respectively. They targeted these regions with repetitive transcranial magnetic stimulation (rTMS) during a brief delay, and found that rTMS stimulation of the STG, but not the middle temporal gyrus, resulted in

impaired recall of non-semantic information. STG hyperactivation during WKM performance in MCI may therefore be indicative of an increased need to rehearse to-be-remembered items in order to maintain normal levels of WKM performance. For example, it is possible that MCI patients engage in increased rehearsal in order to increase their chances of successful encoding; this process may occur as a result of initially poor encoding. Alternatively, WKM-related functional differences in the STG are consistent with histopathological work demonstrating that AD pathology is initially observed in the MTLs, from which it spreads to surrounding brain regions (Alafuzoff et al., 2008; Braak & Braak, 1991). In other words, neuropathology has already begun to spread and have a neurodegenerative effect on areas other than the MTLs in the pre-clinical stages of AD. In this case, hyper-activation of the STG would therefore be a compensatory mechanism for STG dysfunction.

BOLD signal differences during recall were not crucial to the aims of this study since it has been established that episodic memory recall deficits in MCI are associated with BOLD signal differences (Dannhauser et al., 2008; Jin et al., 2012; Kircher et al., 2007; Poettrich et al., 2009). Nevertheless, significantly increased BOLD signals during CWKMS recall were observed for the MCI group in bilateral STG and MTL (Figure 3.4). This indicates that similar cognitive processes occur during the CWKMS recall phase as during the encoding and maintenance phase. Working under the STG framework just discussed, STG differences during recall indicate that MCI patients may be exerting more effort in rehearsing the to-be-remembered letters. This is very plausible given the nature of the recall phase. During recall participants are presented with various probe arrays and must identify which, if any, of the arrays matches the correct sequence of to-be-

remembered letters. As such, they must compare the probes to their own representations which they are likely rehearsing. Significant increases in bilateral ventromedial frontal (VMF) lobe and ACC BOLD signals were also evidenced for the MCI group. VMF and ACC are often associated with decision making and error detection (Bechara et al., 1999; Bechara et al., 2001; Botvinick et al., 2001; MacDonald et al., 2000), respectively; two cognitive functions necessary for performance of the recall phase. It is possible that due to impaired LTM and WKM systems, MCI patients recruit decision making mechanisms to a greater degree to successfully compare their memory traces with relevant information entering into the focus of attention.

Limitations

A well-known problem with conducting MCI research is that MCI is a heterogeneous syndrome which has been classified into several subtypes, with a-MCI being the most prevalent. Subtyping is beneficial for prognosticating progression to a given dementia, for example, those with a-MCI typically advance into AD (Petersen et al., 2004). Partly due to its heterogeneous presentation, however, all MCI subtypes are at risk for conversion to AD or other non-AD dementias (Fischer et al., 2007; Rountree et al., 2007); therefore, we did not restrict our analyses to a specific subtype such as a-MCI. Based on CDR domain scores, though, most MCI patients in the current study appeared to display a primary memory impairment and would therefore be classified as a-MCI.

Varying methods for classifying patients with mild impairments in cognition into MCI, questionable dementia, or very mild dementia have been suggested (e.g., Albert et al., 2011; Chang et al., 2011; Morris, 1993; O'Bryant et al., 2008; O'Bryant et al., 2010;

Petersen et al., 1999). Here, we used a global CDR score of 0.5 to classify individuals as MCI. The use of a global CDR score of 0.5 has been previously supported (Morris, 1993), but the use of this criteria has been debated as some have argued that those with very mild dementia may be grouped into the same category. An alternative staging guideline which has been shown to have good sensitivity and specificity is to assess the sum of boxes (SB) scores of the CDR (O'Bryant et al. 2008; 2010). Using this guideline, those with a GS of 0.5 and SB scores of 0.5-2.0 are classified as questionable dementia or MCI, while those with a GS of 0.5 and SB scores of 2.5-4.0 are classified as very mild dementia. The MCI sample for the current study had a GS of 0.5 and an SB average of 1.16, therefore, the likelihood of having individuals with very mild dementia included in the MCI sample was very low.

An important decision in the analyses was to not control for level of education, even though the MCI group had significantly lower levels of education. It has been shown that individuals presenting with MCI or dementia often have lower levels of education than their age-matched controls (Antilla et al., 2002; Fratiglioni & Wang, 2007; Ngandu et al., 2007; Sattler et al., 2012; Stern et al., 1994). Level of education is often used as a proxy for cognitive reserve, or the ability of the brain to cope with injury by recruiting previously established and efficient processes, or implementing compensatory mechanisms (Stern, 2006). Therefore, level of education serves as a protective factor, such that those with higher levels of education who display similar levels of impairments as their age matched, but lesser educated peers, often exhibit more advanced stages of pathology and degeneration. Consequently, those individuals exhibit greater neuropathological deficits when compared to their healthy, age-matched controls

and statistically controlling for level of education may artificially alter the variance in the functional findings attributable to cognitive impairment.

Lastly, CWKMS performance is an involved process in which retrieval of to-be-remembered information also occurs during the encoding and maintenance phase. This is because the purpose of the distractor is to displace to-be-remembered information from the focus of attention in order to engage WKM and LTM processes rather than just STM. Consequently, it is difficult to associate specific WKM processes with functional activation because of robust recruitment of the WKM system during CWKMS task performance. The robust activation evidenced in both groups is beneficial for between group comparisons, though, as significant differences will be restricted to fewer, possibly more critical regions. In the current study, CWKMS encoding and maintenance differences were restricted to the lateral and medial temporal lobes, rather than including frontal regions as was hypothesized. Therefore, it may be said that use of this CWKMS task allowed us to hone in on regions whose functional activation differences may have the greatest impact upon WKM performance.

Conclusions

CWKMS tasks have been used for a number years in cognitive research (Daneman & Carpenter, 1980; LaPointe & Engle, 1990; Turner & Engle, 1989), but have only recently begun to be used in neuroimaging (Chein et al., 2011; Faraco et al., 2011; Kondo et al., 2004). This is the first study that we are aware of that has used a CWKMS on an impaired population while collecting BOLD data. Between group comparisons demonstrated that the CWKMS task was sensitive to STG and MTL deficits during

encoding and maintenance. These same regions, along with VMF cortex, displayed differential activation during recall. Differences in MTL activation during WKM performance are not surprising given that the WKM system is highly dependent on LTM processes. STG differences, however, are rather novel in the context of WKM and MCI, but fit well within recent frameworks of WKM rehearsal (Acheson et al., 2011; Ravizza et al., 2011) and/or the established idea that AD pathology radiates from the MTLs (Alafuzoff et al., 2008; Braak & Braak, 1991). Further examinations of STG hyper-activity or dysfunction as a biomarker of MCI, its functional relationship with the MTLs during WKM, and its power as a predictor of conversion to AD are warranted.

References

Acheson, D.J., Hamidi, M., Binder, J.R., Postle, B.R., 2011. A common neural substrate for language production and verbal working memory. J Cogn Neurosci 23, 1358-1367.

Alafuzoff, I., Arzberger, T., Al-Sarraj, S., Bodi, I., Bogdanovic, N., Braak, H., Bugiani, O., Del-Tredici, K., Ferrer, I., Gelpi, E., Giaccone, G., Graeber, M.B., Ince, P., Kamphorst, W., King, A., Korkolopoulou, P., Kovacs, G.G., Larionov, S., Meyronet, D., Monoranu, C., Parchi, P., Patsouris, E., Roggendorf, W., Seilhean, D., Tagliavini, F., Stadelmann, C., Streichenberger, N., Thal, D.R., Wharton, S.B., Kretzschmar, H., 2008. Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium. Brain Pathol 18, 484-496.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 270-279.

Alescio-Lautier, B., Michel, B.F., Herrera, C., Elahmadi, A., Chambon, C., Touzet, C., Paban, V., 2007. Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention. Neuropsychologia 45, 1948-1960.

Amaral, D.G., Witter, M.P., 1989. The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 31, 571-591.

Anttila, T., Helkala, E.L., Kivipelto, M., Hallikainen, M., Alhainen, K., Heinonen, H., Mannermaa, A., Tuomilehto, J., Soininen, H., Nissinen, A., 2002. Midlife income, occupation, APOE status, and dementia: a population-based study. Neurology 59, 887-893.

Baddeley, A., Logie, R., Bressi, S., Della Sala, S., Spinnler, H., 1986. Dementia and working memory. Q J Exp Psychol A 38, 603-618.

Baddeley, A.D., Bressi, S., Della Sala, S., Logie, R., Spinnler, H., 1991. The decline of working memory in Alzheimer's disease. A longitudinal study. Brain 114 (Pt 6), 2521-2542.

Baddeley, A.D., Hitch, G., 1974. Working Memory. In: Bower, G.H. (Ed.), The psychology of learning and motivation: Advances in research and theory. Academic Press, New York, pp. 47-89.

Bechara, A., Damasio, H., Damasio, A.R., Lee, G.P., 1999. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci 19, 5473-5481.

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S.W., Nathan, P.E., 2001. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia 39, 376-389.

Belleville, S., Chertkow, H., Gauthier, S., 2007. Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. Neuropsychology 21, 458-469.

Belleville, S., Sylvain-Roy, S., de Boysson, C., Menard, M.C., 2008. Characterizing the memory changes in persons with mild cognitive impairment. Prog Brain Res 169, 365-375.

Blumenfeld, R.S., Ranganath, C., 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci 26, 916-925.

Bokde, A.L., Karmann, M., Born, C., Teipel, S.J., Omerovic, M., Ewers, M., Frodl, T., Meisenzahl, E., Reiser, M., Moller, H.J., Hampel, H., 2010. Altered brain activation during a verbal working memory task in subjects with amnestic mild cognitive impairment. J Alzheimers Dis 21, 103-118.

Bopp, K.L., Verhaeghen, P., 2005. Aging and verbal memory span: a meta-analysis. J Gerontol B Psychol Sci Soc Sci 60, P223-233.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol Rev 108, 624-652.

Bozzali, M., Filippi, M., Magnani, G., Cercignani, M., Franceschi, M., Schiatti, E., Castiglioni, S., Mossini, R., Falautano, M., Scotti, G., Comi, G., Falini, A., 2006. The contribution of voxel-based morphometry in staging patients with mild cognitive impairment. Neurology 67, 453-460.

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., Del Tredici, K., 2006. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 112, 389-404.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82, 239-259.

Brandt, J., Aretouli, E., Neijstrom, E., Samek, J., Manning, K., Albert, M.S., Bandeen-Roche, K., 2009. Selectivity of executive function deficits in mild cognitive impairment. Neuropsychology 23, 607-618.

Broadbent, D.E., 1958. Perception and communication. Pergamon Press, London.

Buchsbaum, B.R., D'Esposito, M., 2008. The search for the phonological store: from loop to convolution. J Cogn Neurosci 20, 762-778.

Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 2001. Prefrontal regions involved in keeping information in and out of mind. Brain 124, 2074-2086.

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging 17, 85-100.

Celone, K.A., Calhoun, V.D., Dickerson, B.C., Atri, A., Chua, E.F., Miller, S.L., DePeau, K., Rentz, D.M., Selkoe, D.J., Blacker, D., Albert, M.S., Sperling, R.A., 2006. Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. J Neurosci 26, 10222-10231.

Chang, Y.L., Bondi, M.W., McEvoy, L.K., Fennema-Notestine, C., Salmon, D.P., Galasko, D., Hagler, D.J., Jr., Dale, A.M., Alzheimer's Disease Neuroimaging, I., 2011. Global clinical dementia rating of 0.5 in MCI masks variability related to level of function. Neurology 76, 652-659.

Chein, J.M., Fiez, J.A., 2001. Dissociation of verbal working memory system components using a delayed serial recall task. Cereb Cortex 11, 1003-1014.

Chein, J.M., Moore, A.B., Conway, A.R., 2011. Domain-general mechanisms of complex working memory span. Neuroimage 54, 550-559.

Colliot, O., Chetelat, G., Chupin, M., Desgranges, B., Magnin, B., Benali, H., Dubois, B., Garnero, L., Eustache, F., Lehericy, S., 2008. Discrimination between Alzheimer disease, mild cognitive impairment, and normal aging by using automated segmentation of the hippocampus. Radiology 248, 194-201.

Conway, A.R., Kane, M.J., Engle, R.W., 2003. Working memory capacity and its relation to general intelligence. Trends Cogn Sci 7, 547-552.

Cowan, N., 2005. Working memory capacity. Psychology Press, New York.

Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci 7, 415-423.

Daneman, M., Carpenter, P.A., 1980. Individual differences in working memory and reading. J VERB LEARN VERB BE 19, 450-466.

Dannhauser, T.M., Shergill, S.S., Stevens, T., Lee, L., Seal, M., Walker, R.W., Walker, Z., 2008. An fMRI study of verbal episodic memory encoding in amnestic mild cognitive impairment. Cortex 44, 869-880.

DeCarli, C., 2003. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2, 15-21.

D'Esposito, M., Postle, B.R., 1999. The dependence of span and delayed-response performance on prefrontal cortex. Neuropsychologia 37, 1303-1315.

Dickerson, B.C., Salat, D.H., Greve, D.N., Chua, E.F., Rand-Giovannetti, E., Rentz, D.M., Bertram, L., Mullin, K., Tanzi, R.E., Blacker, D., Albert, M.S., Sperling, R.A., 2005. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology 65, 404-411.

Du, A.T., Schuff, N., Amend, D., Laakso, M.P., Hsu, Y.Y., Jagust, W.J., Yaffe, K., Kramer, J.H., Reed, B., Norman, D., Chui, H.C., Weiner, M.W., 2001. Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J Neurol Neurosurg Psychiatry 71, 441-447.

Engle, R.W., Kane, M.J., Tuholski, S.W., 1999. Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In: Miyake, A., Shah, P. (Eds.), Models of working memory. Cambridge University Press, Cambridge, pp. 102-134.

Faraco, C.C., Unsworth, N., Langley, J., Terry, D., Li, K., Zhang, D., Liu, T., Miller, L.S., 2011. Complex span tasks and hippocampal recruitment during working memory. Neuroimage 55, 773-787.

Fellgiebel, A., Wille, P., Muller, M.J., Winterer, G., Scheurich, A., Vucurevic, G., Schmidt, L.G., Stoeter, P., 2004. Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. Dement Geriatr Cogn Disord 18, 101-108.

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., Krampla, W., Tragl, K.H., 2007. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. Neurology 68, 288-291.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. J Neurosci 29, 15223-15231.

Fouquet, M., Desgranges, B., La Joie, R., Riviere, D., Mangin, J.F., Landeau, B., Mezenge, F., Pelerin, A., de La Sayette, V., Viader, F., Baron, J.C., Eustache, F.,

Chetelat, G., 2012. Role of hippocampal CA1 atrophy in memory encoding deficits in amnestic Mild Cognitive Impairment. Neuroimage 59, 3309-3315.

Fratiglioni, L., Wang, H.X., 2007. Brain reserve hypothesis in dementia. J Alzheimers Dis 12, 11-22.

Gagnon, L.G., Belleville, S., 2011. Working memory in mild cognitive impairment and Alzheimer's disease: contribution of forgetting and predictive value of complex span tasks. Neuropsychology 25, 226-236.

Gathercole, S.E., Baddeley, A.D., 1993. Working memory and language. Lawrence Erlbaum Associates Ltd., Hove.

Germano, C., Kinsella, G.J., 2005. Working memory and learning in early Alzheimer's disease. Neuropsychol Rev 15, 1-10.

Gomez-Isla, T., Price, J.L., McKeel, D.W., Jr., Morris, J.C., Growdon, J.H., Hyman, B.T., 1996. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci 16, 4491-4500.

Grober, E., Hall, C.B., Lipton, R.B., Zonderman, A.B., Resnick, S.M., Kawas, C., 2008. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Int Neuropsychol Soc 14, 266-278.

Hampstead, B.M., Stringer, A.Y., Stilla, R.F., Amaraneni, A., Sathian, K., 2011. Where did I put that? Patients with amnestic mild cognitive impairment demonstrate widespread reductions in activity during the encoding of ecologically relevant object-location associations. Neuropsychologia 49, 2349-2361.

Hughes, C.P., Berg, L., Danziger, W.L., Coben, L.A., Martin, R.L., 1982. A new clinical scale for the staging of dementia. Br J Psychiatry 140, 566-572.

Insausti, R., 1993. Comparative anatomy of the entorhinal cortex and hippocampus in mammals. Hippocampus 3 Spec No, 19-26.

Jenkinson, M., 2003. A fast, automated, N-dimensional phase-unwrapping algorithm. Magn Reson Med 49, 193-197.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825-841.

Jin, M., Pelak, V.S., Curran, T., Nandy, R.R., Cordes, D., 2012. A preliminary study of functional abnormalities in aMCI subjects during different episodic memory tasks. Magn Reson Imaging 30, 459-470.

Johnson, S.C., Schmitz, T.W., Moritz, C.H., Meyerand, M.E., Rowley, H.A., Alexander, A.L., Hansen, K.W., Gleason, C.E., Carlsson, C.M., Ries, M.L., Asthana, S., Chen, K., Reiman, E.M., Alexander, G.E., 2006. Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment. Neurobiol Aging 27, 1604-1612.

Kane, M.J., Conway, A.R., Miura, T.K., Colflesh, G.J., 2007. Variation in working memory capacity as variation in executive attention and control. In: Conway, A.R., Jarrold, C., Kane, M.J., Miyake, A., Towse, J. (Eds.), Variation in working memory. Oxford University Press, New York, pp. 21-48.

Kane, M.J., Hambrick, D.Z., Tuholski, S.W., Wilhelm, O., Payne, T.W., Engle, R.W., 2004. The generality of working memory capacity: a latent-variable approach to verbal and visuospatial memory span and reasoning. J Exp Psychol Gen 133, 189-217.

Kantarci, K., Avula, R.T., Senjem, L.M., Samikoglu, A.R., Shiung, M.M., Przybelski, S.A., Weigand, S.D., Ward, H.A., Vemuri, P., Knopman, D.S., Boeve, B.F., Petersen, R.C., Jack Jr., C.R., 2009. Diffusion tensor imaging characteristics of amnestic and nonamnestic mild cognitive impairment. Alzheimer's & Dementia 5, P12.

Karas, G., Sluimer, J., Goekoop, R., van der Flier, W., Rombouts, S.A., Vrenken, H., Scheltens, P., Fox, N., Barkhof, F., 2008. Amnestic mild cognitive impairment: structural MR imaging findings predictive of conversion to Alzheimer disease. AJNR Am J Neuroradiol 29, 944-949.

Kessels, R.P., Meulenbroek, O., Fernandez, G., Olde Rikkert, M.G., 2010. Spatial working memory in aging and mild cognitive impairment: effects of task load and contextual cueing. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 17, 556-574.

Killiany, R.J., Hyman, B.T., Gomez-Isla, T., Moss, M.B., Kikinis, R., Jolesz, F., Tanzi, R., Jones, K., Albert, M.S., 2002. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 58, 1188-1196.

Kircher, T.T., Weis, S., Freymann, K., Erb, M., Jessen, F., Grodd, W., Heun, R., Leube, D.T., 2007. Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding. J Neurol Neurosurg Psychiatry 78, 812-818.

Kochan, N.A., Breakspear, M., Slavin, M.J., Valenzuela, M., McCraw, S., Brodaty, H., Sachdev, P.S., 2010. Functional alterations in brain activation and deactivation in

mild cognitive impairment in response to a graded working memory challenge. Dement Geriatr Cogn Disord 30, 553-568.

Kochan, N.A., Breakspear, M., Valenzuela, M., Slavin, M.J., Brodaty, H., Wen, W., Trollor, J.N., Turner, A., Crawford, J.D., Sachdev, P.S., 2011. Cortical responses to a graded working memory challenge predict functional decline in mild cognitive impairment. Biol Psychiatry 70, 123-130.

Kondo, H., Morishita, M., Osaka, N., Osaka, M., Fukuyama, H., Shibasaki, H., 2004. Functional roles of the cingulo-frontal network in performance on working memory. Neuroimage 21, 2-14.

LaPointe, L.B., Engle, R.W., 1990. Simplex and complex word spans as measures of working memory capacity. J Exp Psychol Learn 16, 1118-1133.

MacDonald, A.W., 3rd, Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835-1838.

Machulda, M.M., Ward, H.A., Borowski, B., Gunter, J.L., Cha, R.H., O'Brien, P.C., Petersen, R.C., Boeve, B.F., Knopman, D., Tang-Wai, D.F., Ivnik, R.J., Smith, G.E., Tangalos, E.G., Jack, C.R., Jr., 2003. Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. Neurology 61, 500-506.

McElree, B., 2006. Accessing recent events. In: Ross, B.H. (Ed.), The psychology of learning and motivation. Academic Press, San Diego.

Meyer, J.S., Huang, J., Chowdhury, M., 2005. MRI abnormalities associated with mild cognitive impairments of vascular (VMCI) versus neurodegenerative (NMCI) types prodromal for vascular and Alzheimer's dementias. Curr Alzheimer Res 2, 579-585.

Miller, S.L., Fenstermacher, E., Bates, J., Blacker, D., Sperling, R.A., Dickerson, B.C., 2008. Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline. J Neurol Neurosurg Psychiatry 79, 630-635.

Milner, B., 1972. Disorders of learning and memory after temporal lobe lesions in man. Clin Neurosurg 19, 421-446.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412-2414.

Morris, J.C., 1997. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 9 Suppl 1, 173-176; discussion 177-178.

Ngandu, T., von Strauss, E., Helkala, E.L., Winblad, B., Nissinen, A., Tuomilehto, J., Soininen, H., Kivipelto, M., 2007. Education and dementia: what lies behind the association? Neurology 69, 1442-1450.

Oberauer, K., 2002. Access to information in working memory: exploring the focus of attention. J Exp Psychol Learn Mem Cogn 28, 411-421.

O'Bryant, S.E., Lacritz, L.H., Hall, J., Waring, S.C., Chan, W., Khodr, Z.G., Massman, P.J., Hobson, V., Cullum, C.M., 2010. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 67, 746-749.

O'Bryant, S.E., Waring, S.C., Cullum, C.M., Hall, J., Lacritz, L., Massman, P.J., Lupo, P.J., Reisch, J.S., Doody, R., 2008. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol 65, 1091-1095.

Panza, F., D'Introno, A., Colacicco, A.M., Capurso, C., Del Parigi, A., Caselli, R.J., Pilotto, A., Argentieri, G., Scapicchio, P.L., Scafato, E., Capurso, A., Solfrizzi, V., 2005. Current epidemiology of mild cognitive impairment and other predementia syndromes. Am J Geriatr Psychiatry 13, 633-644.

Petersen, R.C., Bennett, D., 2005. Mild cognitive impairment: is it Alzheimer's disease or not? J Alzheimers Dis 7, 241-245; discussion 255-262.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., Winblad, B., 2001. Current concepts in mild cognitive impairment. Arch Neurol 58, 1985-1992.

Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D.R., Ofstedal, M.B., Burke, J.R., Hurd, M.D., Potter, G.G., Rodgers, W.L., Steffens, D.C., Willis, R.J., Wallace, R.B., 2007. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 29, 125-132.

Poettrich, K., Weiss, P.H., Werner, A., Lux, S., Donix, M., Gerber, J., von Kummer, R., Fink, G.R., Holthoff, V.A., 2009. Altered neural network supporting declarative long-term memory in mild cognitive impairment. Neurobiol Aging 30, 284-298.

Postle, B.R., Druzgal, T.J., D'Esposito, M., 2003. Seeking the neural substrates of visual working memory storage. Cortex 39, 927-946.

Rapp, M.A., Reischies, F.M., 2005. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). Am J Geriatr Psychiatry 13, 134-141.

Ravizza, S.M., Hazeltine, E., Ruiz, S., Zhu, D.C., 2011. Left TPJ activity in verbal working memory: implications for storage- and sensory-specific models of short term memory. Neuroimage 55, 1836-1846.

Roach, E.S., 2005. Treating mild cognitive impairment: The absence of evidence. Arch Neurol 62, 1167.

Rosen, V.M., Bergeson, J.L., Putnam, K., Harwell, A., Sunderland, T., 2002. Working memory and apolipoprotein E: what's the connection? Neuropsychologia 40, 2226-2233.

Rountree, S.D., Waring, S.C., Chan, W.C., Lupo, P.J., Darby, E.J., Doody, R.S., 2007. Importance of subtle amnestic and nonamnestic deficits in mild cognitive impairment: prognosis and conversion to dementia. Dement Geriatr Cogn Disord 24, 476-482.

Sattler, C., Toro, P., Schonknecht, P., Schroder, J., 2012. Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. Psychiatry Res 196, 90-95.

Saunders, N.L., Summers, M.J., 2011. Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. Neuropsychology 25, 237-248.

Small, S.A., Schobel, S.A., Buxton, R.B., Witter, M.P., Barnes, C.A., 2011. A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nat Rev Neurosci 12, 585-601.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum Brain Mapp 17, 143-155.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 Suppl 1, S208-219.

Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu Rev Neurosci 27, 279-306.

Stern, Y., 2006. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord 20, 112-117.

Stern, Y., Gurland, B., Tatemichi, T.K., Tang, M.X., Wilder, D., Mayeux, R., 1994. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 271, 1004-1010.

Unsworth, N., Engle, R.W., 2007. The nature of individual differences in working memory capacity: active maintenance in primary memory and controlled search from secondary memory. Psychol Rev 114, 104-132.

Unsworth, N., Engle, R.W., 2007. On the division of short-term and working memory: an examination of simple and complex span and their relation to higher order abilities. Psychol Bull 133, 1038-1066.

West, M.J., Coleman, P.D., Flood, D.G., Troncoso, J.C., 1994. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. Lancet 344, 769-772.

White, K.G., Ruske, A.C., 2002. Memory deficits in Alzheimer's disease: the encoding hypothesis and cholinergic function. Psychon Bull Rev 9, 426-437.

Wolf, H., Grunwald, M., Kruggel, F., Riedel-Heller, S.G., Angerhofer, S., Hojjatoleslami, A., Hensel, A., Arendt, T., Gertz, H., 2001. Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly. Neurobiol Aging 22, 177-186.

Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. Neuroimage 45, S173-186.

Yetkin, F.Z., Rosenberg, R.N., Weiner, M.F., Purdy, P.D., Cullum, C.M., 2006. FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur Radiol 16, 193-206.

Zhuang, L., Wen, W., Zhu, W., Trollor, J., Kochan, N., Crawford, J., Reppermund, S., Brodaty, H., Sachdev, P., 2010. White matter integrity in mild cognitive impairment: a tract-based spatial statistics study. Neuroimage 53, 16-25.

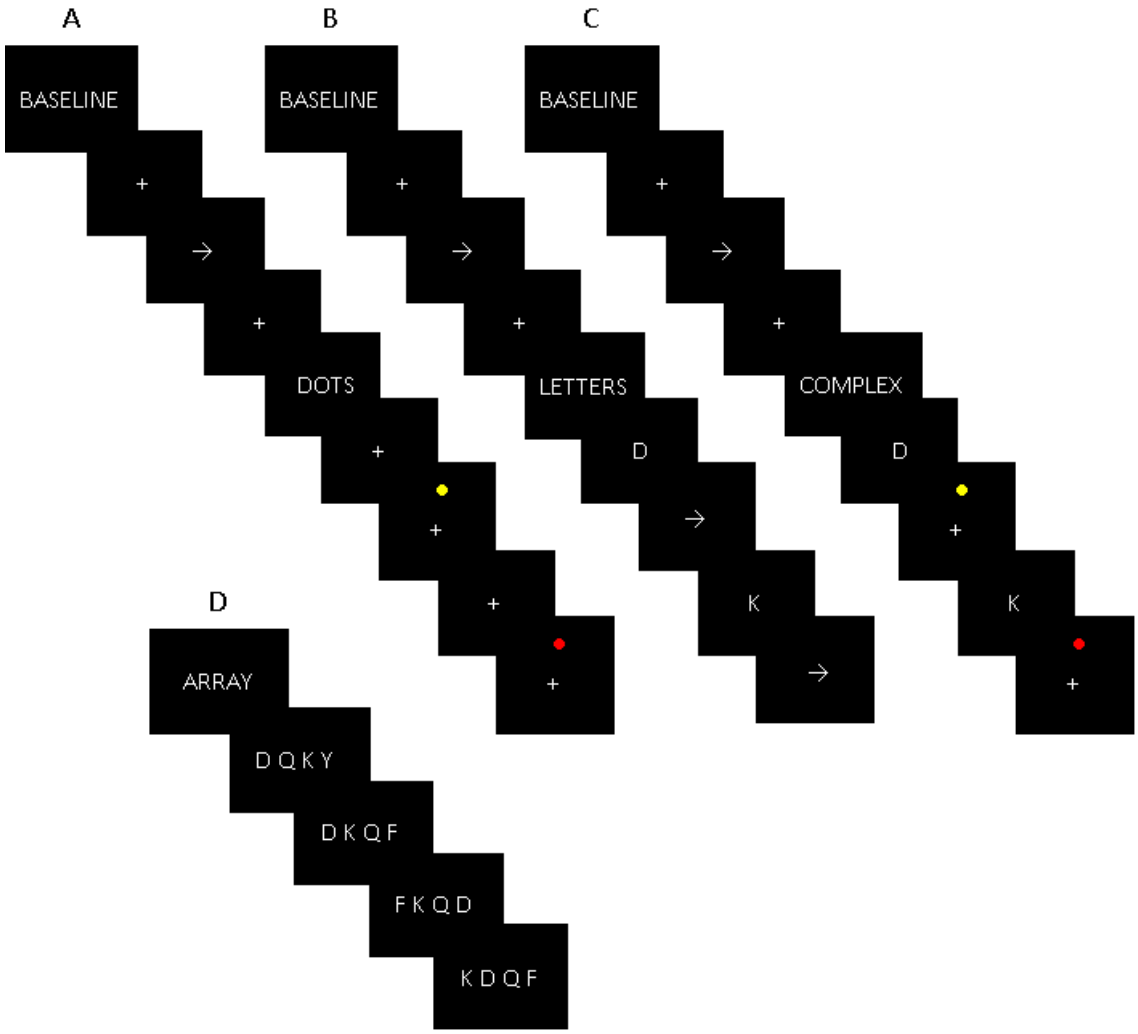

Figure 3.1. Depiction of distractor, verbal STM, and CWKMS task. For all tasks the baseline block is identical, participants are presented with a cue indicating the start of the baseline block and then have to press when they see the right-pointing arrow, A.Distractor task. Participants are cued to the start of the block by the word “DOTS” and then have to press with they see a red dot. B. Verbal STM. Participants are cued to the start of the block by the word “LETTERS.” They have to remember the letters presented (total of 4) in the order of presentation and must press when they see an arrow. C. CWKMS task. Participants are cued to the start of the block by the word “COMPLEX.” As in the previous trial they must remember the letters in order of presentation, but in between each letter presentation they must now attend to the presentation of a red dot. D. Array. Participants are cued to the start of the block by the word “ARRAY.” The array/retrieval condition proceeds both the verbal STM and CWKMS tasks. Participants must identify which of the arrays accurately represents the order of presentation of the letters. Please refer to the Task and stimuli section in the methods for further details.

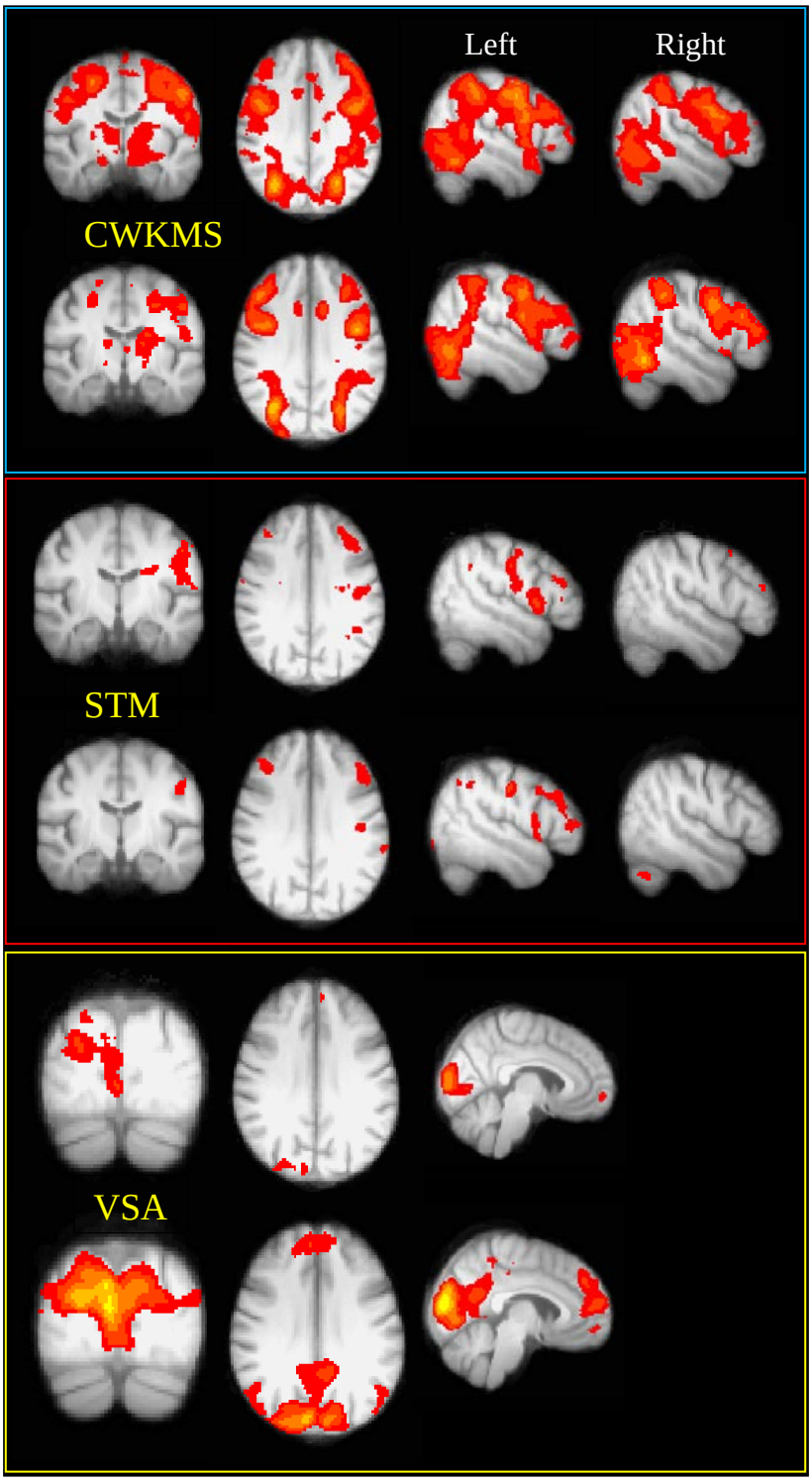

Figure 3.2. Within group activation. For each task at Z > 4.5 and p < 0.05. The top row of each set is the activation map for the MCI group, the bottow row of each set is the activation map for the healthy, older adults. Coronal and axial images are presented in radiologic orientation. The two largest cluster sizes for each task and group are as

follows. CWKMS task: MCI 1) 60957, 2) 416; CON 1) 27901. STM task: MCI 1) 1133, 2) 811; CON 1) 796, 2) 673. VSA task: MCI 1) 1704, 2) 152; CON 1) 8958, 2) 2326.

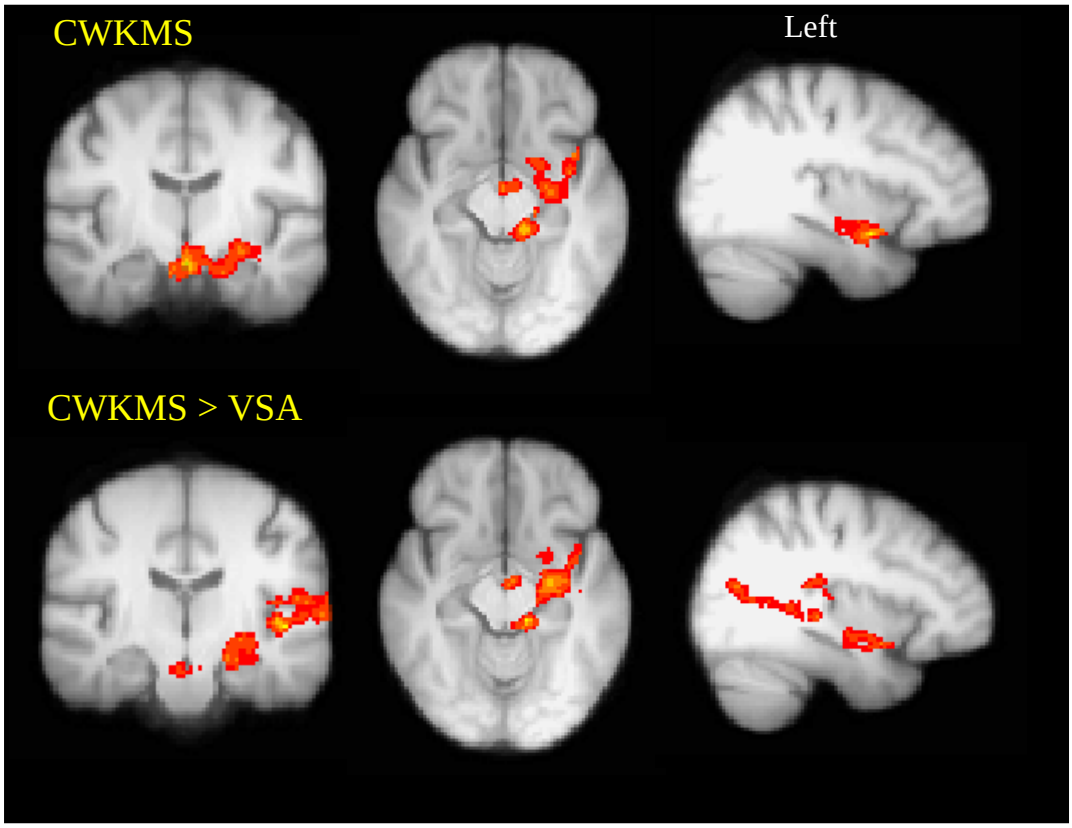

Figure 3.3. Between group CWKMS differences. MCI – CON contrasts for CWKMS encoding and maintenance block, and CWKMS encoding and maintenance > VSA; Z > 2.3 and $p < 0.05$. The latter contrast is designed to focus on working memory encoding and maintenance. Both contrats demonstrated activation in the hippocampal formation, while CWKMS > VSA additionally demonstrated activation in the STG.

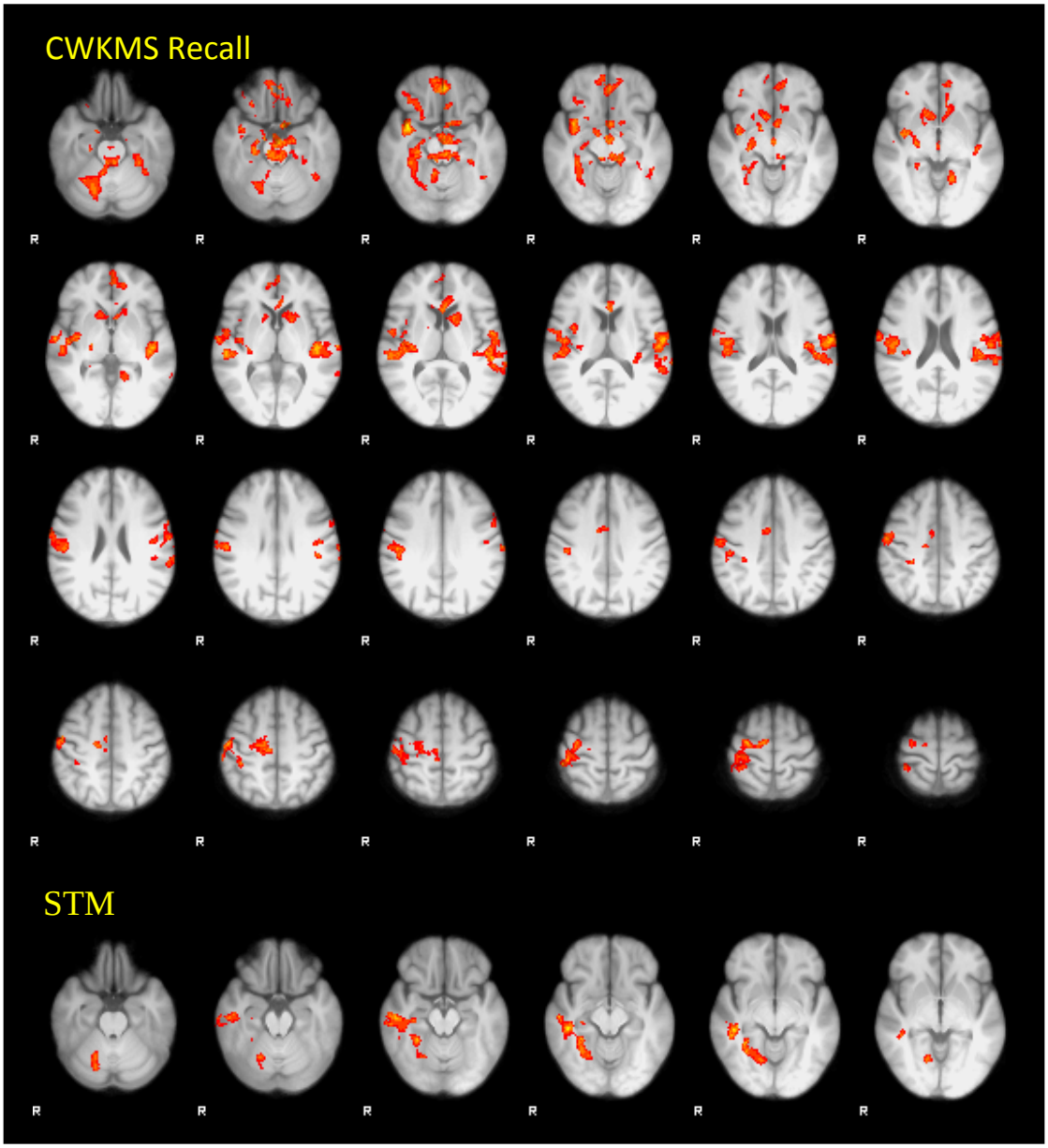

Figure 3.4. Between group recall differences. MCI – CON differences for CWKMS and STM recall; $Z > 2.3$ and $p < 0.05$. MCI participants demonstrated significantly higher level of activation during CWKMS recall in areas activated during encoding and maintenance, but also in frontal regions associated with decision making and error detection, i.e., ventromedial prefrontal and anterior cingulate cortices, respectively.

Table 3.1
Demographic and behavioral data.

	Control Group Avg.	MCI Group Avg.	*t*-Test	p value
Age	74.17 (5.50)	75.13 (6.53)	0.50	0.619
Education (yrs)	16.96 (2.33)	14.19 (3.47)	3.03	0.004*
CWKMS Recall RT	1460.69 (332.06)	1527.09 (244.99)	0.684	0.498
CWKMS Recall correct	6.50 (0.72)	6.19 (1.33)	0.963	0.342
CWKMS Dot RT	669.61 (119.38)	673.34 (81.08)	0.109	0.914
Verbal STM Recall RT	1477.71 (384.48)	1763.27 (339.07)	2.409	0.021*
Verbal STM Recall correct	6.66 (0.70)	5.69 (2.08)	2.134	0.039*
VSA Dot RT	572.05 (97.05)	580.10 (53.01)	0.302	0.764

*Significant differences between groups.

Table 3.2
Areas of greater MCI group activation for CWKMS.

Cluster	Region	Coordinates in mm, MNI			Z-score
		x	*y*	*z*	
1	L Parahippocampal Gyrus, Posterior	-34	0	-16	3.61
	L Parahippocampal Gyrus, Anterior	-12	-32	-14	3.55
	L Insular Cortex	-38	-2	-12	2.77
	L Amygdala	-26	-12	-12	2.75
	L Hippocampus	-14	-14	-20	2.72
	L Temporal Pole	-46	10	-16	2.57

$Z > 2.0$, $p = .05$.

Table 3.3

Areas of greater MCI group activation for CWKMS > VSA.

Cluster	Region	Coordinates in mm, MNI			Z-score
		x	*y*	*z*	
1	L Superior Temporal Gyrus, Posterior	-70	-36	10	4.11
	L Heschl's Gyrus	-44	-20	2	3.77
	L Lateral Occipital Cortex	-48	-66	8	3.38
	L Parietal Operculum	-42	-32	20	3.31
	L Central Operculum	-44	-16	12	3.28
	L Supramarginal Gyrus	-58	-46	12	3.22
	L Planum Temporale	-58	-24	6	2.88
	L Insula	-40	-10	2	2.51
2	L Amygdala	-26	-10	-10	3.81
	L Parahippocampal Gyrus, Posterior	-16	-34	-10	3.67
	L Hippocampus	-22	-16	-14	3.51
	L Insula	-36	4	-14	3.06

$Z > 2.3$, $p = .05$.

Table 3.4
Areas of greater MCI group activation for CWKMS recall.

Cluster	Region	Coordinates in mm, MNI			Z-score
		x	*y*	*z*	
1	R Insula	38	0	-16	3.79
	R Superior Temporal Gyrus	56	-28	6	3.52
	R Central Operculum	52	-18	22	3.35
	R Planum Temporale	62	-10	0	3.34
	R Hippocampus	28	-24	-18	3.21
	R Postcentral Gyrus	50	-20	32	3.21
	L Lingual Gyrus	-14	-54	-4	3.18
	R Parietal Operculum	52	-26	12	3.15
	L Parahippocampal Gyrus, Posterior	-14	-34	-12	3.13
	L Hippocampus	-16	-16	-22	3.12
	R Heschl's Gyrus	46	-14	0	3.11
	L Parahippocampal Gyrus, Anterior	24	-22	-22	3.07
2	L Postcentral Gyrus	-62	-12	14	3.51
	L Central Operculum	-56	-16	18	3.42
	L Planum Temporale	-64	-36	18	3.40
	L Superior Temporal Gyrus, Posterior	-66	-18	4	3.37
	L Heschl's Gyrus	-44	-20	4	3.33
	L Parietal Operculum	-46	-26	16	3.21
	L Insula	-36	-18	16	3.20
3	R Precentral Gyrus	30	-12	64	3.29
	R Postcentral Gyrus	44	-32	60	3.23
	R Supplementary Motor Cortex	8	-12	62	3.13
	R Anterior Cingulate Cortex	8	2	38	2.99
	R Superior Parietal Lobule	32	-40	62	2.96
	R Supramarginal Gyrus	60	-30	52	2.82
4	L Frontal Medial Cortex	-2	44	-16	3.37
	L/R Anterior Cingulate Cortex	0	28	10	3.32
	R Frontal Medial Cortex	4	44	-18	3.18
	L/R Paracingulate Gyrus	0	52	4	3.17
	L Subcallosal Cortex	-6	24	-18	3.12
	L Frontal Orbital Cortex	-14	6	-20	2.98
	L Caudate	-16	14	6	2.95
	L Frontal Pole	-2	56	2	2.92

$Z > 2.3$, $p = .05$.

Table 3.5
Areas of greater MCI group activationfor STM recall.

Cluster	Region	Coordinates in mm, MNI			Z-score
		x	*y*	*z*	
1	R Temporal Occipital Fusiform Cortex	32	-46	-10	3.32
	R Middle Temporal Gyrus, Posterior	56	-18	-12	3.12
	R Lingual Gyrus	16	-64	-6	3.04
	R Hippocampus	34	-22	-16	2.77

Z > 2.3, $p = .05$.

CHAPTER 4

RBANS DELAYED MEMORY SCORES CORRELATE WITH WIDESPREAD WHITE MATTER DIFFUSIVITY CHANGES IN MILD COGNITIVE IMPAIRMENT[1]

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Abstract

Mild cognitive impairment (MCI) is often characterized by a primary impairment in memory, but may have a heterogeneous presentation. Consequently, there is a need to establish reliable biomarkers of MCI that may aid in increasing prognostic accuracy. Diffusion tensor imaging (DTI) studies have established that white matter degeneration is evidenced in MCI patients, but areas of degeneration across studies are variable. In order to establish reliable biomarkers of MCI white matter neurodegeneration it may be to beneficial examine the relationships between DTI diffusivity indices and cognitive performance. In this study we correlated domain indices of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) with DTI indices of diffusivity. Results did not demonstrate significant between-groups differences, but significant widespread correlations between axial, radial, and mean diffusivity and delayed memory scores were evidenced for the MCI group. Correlations were evidenced along the superior longitudinal, fronto-occipital, and inferior longitudinal fasciculi, the hippocampus, internal capsule, and the corpus callosum. Neurodegeneration along associative fronto-parietal pathways may be linked to deficits in working memory and long-term representations in MCI. Furthermore, a significant interaction effect was evidenced between radial diffusivity and delayed memory with respect to group. These interaction effects were evidenced along the pathways just mentioned, except for the hippocampus, and along the uncinate fasciculus, external capsule, and cingulum bundle. Radial diffusivity interactions along these late-myelinating pathways may support the idea that neurodegeneration in MCI / Alzheimer's disease occurs through retrogenesis.

Introduction

White matter (WM) degeneration in those with Alzheimer's disease (AD) has been well documented through postmortem examinations, magnetic resonance imaging (MRI), and volumetric measures (e.g., Gold et al., 2007; Kavcic et al., 2008; Rose et al., 2008; Salat et al., 2009; Yasmin et al., 2008). Less clear is the extent of WM degeneration in those with mild cognitive impairment (MCI). While AD is characterized by significant deficits in memory and executive functioning, MCI, as the name suggests, is characterized by mild impairments in cognition and is often viewed as a heterogeneous condition which precedes the onset of dementia (Albert et al., 2011; Petersen et al., 2001; Petersen & Bennett, 2005). Typical estimated yearly conversion rates of MCI to dementia, from both clinic and population based studies, range from 5-15% (DeCarli, 2003; Panza et al., 2005; Petersen, 2004; Roach, 2005). Establishing associations between WM degeneration and cognitive impairment in MCI patients is therefore crucial to delineating the disease process in AD and developing treatments which may delay its onset.

Currently, one of the most popular means by which to investigate WM changes is through diffusion tensor imaging (DTI). DTI is an MRI technique from which scalar indices of water diffusion, thought to reflect varying aspects of WM integrity, can be calculated. These indices are calculated from the tensor eigenvalues ($\lambda 1$, $\lambda 2$, and $\lambda 3$), which describe the strength of diffusion along the corresponding axes or eigenvectors (v1, v2, and v3). Axial diffusivity (DA) is the principal eigenvalue ($\lambda 1$) and is assumed to contribute information regarding the integrity of axons (Glenn et al., 2003) or changes in the extra-axonal/extracellular space (Beaulieu and Allen, 1994). In contrast, radial

diffusivity (DR) is the average of the two remaining eigenvalues ([λ2+λ3]/2) and is assumed to characterize changes associated with myelination or glial cell morphology (Song et al., 2002, 2003, 2005). Mean diffusivity (MD) is the average of all three eigenvectors and provides an all-round descriptor of the degree of diffusivity within the region (Pierpaoli et al., 1996), where increased diffusivity may indicate a decrease in cellular membrane density (Beaulieu, 2002). Lastly, fractional anisotropy (FA) indicates how biased diffusion is along the primary eigenvector; in other words, it is the ratio of the tensor's anisotropy to the whole tensor (Melhem et al., 2002), and is used as an index of overall WM health or integrity (Beaulieu et al., 1996), with reduced anisotropy also being indicative of reduced WM integrity.

Due to the fact that FA and MD are the most common measures examined, past studies of WM differences in MCI and AD have reported anisotropy and diffusivity differences across frontal, parietal, temporal, and/or medial temporal lobe WM (e.g., Bai et al., 2009; Bozzali et al., 2002; Chen et al., 2009; Chua et al., 2008; Fellgiebel et al., 2004; Liu et al., 2011; Medina et al., 2006; Muller et al., 2007; Salat et al., 2009; Salat et al., 2010;). A recent meta-analysis (Sexton et al., 2011) revealed medium to high effect sizes for FA and MD changes across these regions, as well as across specific WM pathways including the posterior cingulum, superior longitudinal fasciculus, and splenium and genu of the corpus callosum, in both AD and MCI. Of note is that a significant degree of effect size heterogeneity was detected in 5 out of 13 group comparisons for FA in AD and 7 out of 9 group comparisons for FA in MCI; MD only displayed a significant heterogeneity for 3 out of 8 comparisons for MCI. Such findings

not only highlight the fact that MCI is a neurodegeneratively heterogeneous condition, but also point out the variability inherent to measures such as FA and possibly MD.

Part of the reason for the heterogeneity of FA and MD findings is that they are inherently limited by the tensor model. In voxels where fibers cross or diverge, for example, a tensor model is unable to accurately describe the diffusion or anisotropy characteristics of the fibers within that region. As a result, all eigenvalues are affected and FA and MD are especially prone to distortion since they are calculated from all three eigenvalues (Alexander et al., 2007; Vos et al., 2012). Furthermore, because of this dependence on all three eigenvalues they are less sensitive to specific aspects of WM degeneration. FA may also lack sensitivity to structural differences in cases where all three eigenvalues change proportionally (Acosta-Cabronero et al., 2010). Previous work has shown that WM changes in early AD are likely to produce proportional changes along all three eigenvectors as FA was grossly insensitive to changes that were evidenced through analysis of DA, DR, and MD (Acosta-Cabronero et al., 2010); DR and MD were also sensitive to WM changes in AD and amnestic MCI (aMCI) in regions where FA differences were not detected (Bosch et al., 2012). Therefore, it may be more fruitful to examine diffusivity measures, rather than FA, when studying MCI.

To gain further insight into the implications of neurodegeneration in MCI and AD, though, associations between indices of WM degeneration and cognition should also be established. Currently, correlations between cognitive performance in MCI/AD and DTI measures have been explored a handful of times (e.g., Bozzali et al., 2002; Bosch et al., 2012; Chen et al., 2007; Fjell et al., 2009; Heo et al., 2009; Muller et al., 2007); with most of these studies having used the Mini Mental State Examination (MMSE; Folstein

et al., 1975), a brief questionnaire designed to yield an overall assessment of cognitive functioning. Even though the MMSE is commonly used in clinical practice to identify AD, it is not as sensitive to MCI (Nasreddine et al., 2005; Tomabaugh et al., 1992; Wind et al., 1997).

MCI has traditionally been associated with a primary episodic memory deficit (Albert et al., 2011; Petersen et al., 2001), but recent evidence suggests that episodic deficits may actually be preceded by more subtle changes in cognition due to impaired language, attentional, executive functioning, and working memory abilities (Cuetos et al., 2007; Grober et al., 2008; Rapp & Reischies, 2005), and that deficits in these domains are actually characteristic of preclinical AD (Twamley et al., 2006). In associating DTI derived measures with cognitive functioning in MCI, it may be useful to examine neuropsychological batteries of clinical utility which assess various domains. One well-known battery which may prove to be useful in this respect is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998). The RBANS, which was designed for the longitudinal assessment of dementia, provides indices for immediate memory (IM), delayed memory (DM), attention (ATT), language (LAN), and visuospatial/constructional (VSC) abilities; most of which can be impaired in MCI. Initial assessment of the RBANS as a diagnostic tool for AD found that sensitivity and specificity were at 90% (Randolph et al., 1998). It has also been shown to be useful in evaluating MCI, though this has been somewhat varied. For example, (Duff et al., 2010) found that specificity values for all memory-related subtests and indices were 0.82 or higher, but sensitivity values were poor. A caveat with these findings is that only those previously diagnosed with a primary memory impairment, i.e., aMCI, were examined.

Clark et al. (2010), however, found that percent retention scores on RBANS List Learning and Story Memory demonstrated excellent specificity and sensitivity in distinguishing those with MCI from controls and AD patients.

The aim of the current study was to examine whether different cognitive processes as measured by the RBANS index scores were associated with WM degeneration in MCI. Based on the cognitive impairments evidenced in MCI, it was expected that IM, DM, ATT, and LAN scores would be correlated with diffusivity indices (DA, DR, and MD) in areas of WM degeneration. Specifically: 1) DM scores should negatively correlate with diffusivity indices of the hippocampus, since it is critical to long term memory functioning (e.g., Milner, 1972, Squire et al., 2004)) and affected in MCI (Colliot et al., 2008; Du et al., 2001; Killiany et al., 2002; Wolf et al., 2001),. 2) DM, IM, and ATT indices, whose sub-tests all appear to rely on some aspect of working memory functioning, should be negatively correlated with diffusivity indices in fasciculi connecting frontal and parietal cortices, as these regions are necessary for proper working memory functioning (Blumenfeld & Ranganath, 2006; Bunge et al., 2001; Chein & Feiz, 2001; Curtis & D'Esposito, 2003; D'Esposito & Postle, 1999; Postle et al., 2003); the most prominent fasciculi extending between these regions are the superior longitudinal fasciculus (SLF) and the fronto-occipital fasciculus (FOF). 3) LAN scores, which are heavily dependent on semantic fluency, should be negatively correlated with WM diffusivity indices in WM pathways coursing through the temporal lobe, as it is involved in speech production, language processing, and object fluency (Fama et al., 2000; Hickok, 2001; Hickok, 2009; Levelt et al., 1998).

Methods

Participants

In total, 52 older adults were recruited from the local community through newspaper advertisements and community engagement. Community interactions included giving "Brain Health" talks at various private and public organizations and centers, including assisted living facilities, caregiver support groups, and the local public library. Following these talks participants were informed of the details of the study and were given flyers with the appropriate contact information.

Of the 52 participants that were recruited for the study, 40 (24 controls, 16 MCI) were included in the current analyses; 6 participants were identified with AD and 6 participants were not able to complete the entire MR scanning protocol.

Inclusion criteria

Before partaking in the study, participants underwent an initial phone screen. Inclusion criteria included compatibility with the MRI environment, between 65 – 85 years of age, confirmation of a reliable collateral, literate, and no history of a neurological disorder. Participants who enlisted in the study were screened once more upon arriving on the first day of testing. Upon completion all were given $100 for participation. Additionally, upon their or the collateral's request a contact sheet with referral sources for additional cognitive assessment was provided.

Measures

Participants and collaterals were interviewed with the Clinical Dementia Rating (CDR) scale, a semi-structured interview designed to assess an individual's level of dementia-related impairment. The CDR obtains collateral-based information regarding the individual being assessed, in this case the participant, and also asks the collateral to recall and detail two recent events in order to test the participant's LTM. Information acquired from both parties is divided into six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Hughes et al., 1982). Each domain is scored individually on a five-point impairment scale (i.e., 0.0 none, 0.5 questionable, 1.0 mild, 2.0 moderate, 3.0 severe), except personal care, which is scored on a four-point scale (i.e., 0.0 none, 1.0 mild, 2.0 moderate, 3.0 severe), using a set of criteria and clinical judgment. Scores are tallied based on an algorithm (Morris, 1993) to arrive at a Global CDR score. The global score is also assessed on the above five-point scale and indicates degree of dementia (Morris, 1997). The diagnosis of MCI has been supported by a CDR global score of 0.5 (Morris, 1993).

MRI acquisition

All scans were acquired using a General Electric (GE; Waukesha, WI) Signa HDx 3T MRI system. 3D structural scans were acquired using a fast spoiled gradient recalled echo (FSPGR) protocol; TE = min full, TR = 7.5 ms, flip angle = 20°, 180 axial slices, slice thickness = 1 mm, and FOV = 256 x 256 mm. Diffusion weighted imaging (DWIs) scans were acquired using a single-shot diffusion-weighted SE-EPI sequence following the same orientation and anatomical coverage of the functional scans; TE = min full, TR

= 15000 ms, 90° RF pulse, 60 interleaved slices, slice gap = 0 mm, 2 mm isotropic voxels, acquisition matrix = 128 x 128, FOV = 256 x 256 mm, parallel acceleration factor = 2, b-value: 1000, and 30 optimized gradient directions with 3 b0 images. Total scan time for the DTI acquisition was 9 min and 38 s. Two pairs of magnitude and phase images were acquired for fieldmap-based unwarping of DWIs; acquisition for each pair of images took 1 min and 40 s.

Image processing

All images were processed using the FMRIB Software Library (FSL; Smith et al., 2004; Woolrich et al., 2009). Before analyses, data were converted from their native GE DICOM format to NIFTI format using the dcm2nii conversion tool (Rorden, 2007). After conversion, fieldmaps were produced to correct for the inherent distortion of the echo planar images. Fieldmaps were calculated using FSL's PRELUDE and FUGUE (Jenkinson, 2003) programs. DWI images were pre-processed by applying the FMRIB Diffusion Toolbox (FDT; Behrens et al., 2003) eddy current correction tool, motion corrected using the first b0 image as a reference, brain extracted using BET, and then distortion corrected using the calculated fieldmaps. Diffusion tensors were then estimated using DTIFIT.

To enhance the ability to detect diffusivity differences in MCI, Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) were employed. TBSS attempts to alleviate many of the problems associated with standard voxel-based approaches by initially optimizing registration of the FA images to standard MNI space. For this study, each subjects' FA images were aligned to each other in order to identify the subject most

representative of the entire sample and use that image as an initial target image for the sample; this image was then affine registered to MNI space. The remaining FA images were then warped to MNI space by combining the non-linear warp used to register them to the initial target image with the affine transformation of the target image to MNI space. TBSS further attempts to correct for subject mis-registration and consequent variability by producing a mean FA image and skeletonizing it. Each subject's FA data were skeletonized by projecting the nearest maximum FA values onto the skeleton.

Statistical analyses

Analyses of the skeletonized images were carried out using FSL's Randomise tool (Nichols and Holmes, 2002), which performs nonparametric, permutation-based testing. In order to enhance detection of diffusivity differences between groups, threshold-free cluster-enhancement (TFCE; enhanced for diffusion data) was employed. TFCE relies on neighborhood information, like cluster based thresholding, but is thought to be superior as an initial cluster threshold does not have to be set thereby minimizing the problem of overlooking the true signal. For each instance of Randomise, 5,000 permutations were run. After the t-statistics were calculated at each voxel, the appropriate TFCE p-values were calculated for each voxel. Any significant differences were identified by voxels where $p<0.05$. For each group, DA, DR, and MD were separately correlated with each index score of the RBANS. An interaction effect analysis was conducted to determine whether group categorization moderated the relationship between diffusivity indices and RBANS scores.

Results

Sample characteristics

Demographic information and test scores are presented in Table 4.1. Mean participant age did not differ between groups, but the control group had significantly more years of education ($p<0.0044$). RBANS scores for the MCI group were significantly lower for IM ($p<0.0013$), ATT ($p<0.0033$), DM ($p<0.0020$), and LAN ($p<0.0034$) indices, but not for VSC ($p<0.0935$).

Within group correlations

Within the MCI group, significant negative correlations ($p<0.05$) between the RBANS delayed memory (DM) index were found in relation to axial diffusivity (DA), radial diffusivity (DR), and mean diffusivity (MD; all in Fig. 4.1). These negative correlations were evidenced along many of the same pathways and included bilateral superior longitudinal fasciculus (SLF), fronto-occipital fasciculus (FOF), and inferior longitudinal fasciculus (ILF), and the genu, body, and splenium of the corpus callosum. Negative correlations ($p<0.05$) between DM and DA and MD were evidenced along the left hippocampal formation. Negative correlations ($p<0.05$) were also found between the immediate memory (IM) index and DA (Fig. 4.2). Areas of significant correlations are detailed in Table 4.2. IM correlations with DA were also evidenced along many of these same pathways, except that correlations were restricted to the left hemisphere and did not include the hippocampal formation (Table 4.2).

For WM pathways that evidenced DM correlations with both DA and DR, and for which an appropriate mask from the John Hopkins University white matter tractography

atlas existed, regression coefficients were compared to determine if they were significantly different. This was done by masking the WM pathway of interest, extracting DA and DR values for every MCI subject in voxels where the group correlations were significant, and calculating the mean for each pathway for each subject. Comparisons were made for bilateral FOF and SLF, and right ILF. Regression coefficients were not significantly different between DA and DR for any of these WM pathways (Fig. 4.3).

Negative correlations between ATT scores and fronto-parietal fasciculi and between LAN scores and temporal lobe WM pathways, such as the arcuate fasciculus or ILF were not evidenced. Furthermore, no significant correlations were evidenced between any of the RBANS indices and diffusivity values in the TBSS skeleton for the control group.

Between group differences and interactions

On the skeletonized TBSS data, no significant ($p<0.05$) between group differences in WM diffusivity were detected between controls and those with MCI. A significant interaction effect ($p<0.05$), though, was found between DM scores and DR in regards to group (Fig. 4.4). Significant interaction effects were evidenced along many fiber pathways (Table 4.2), including bilateral SLF, FOF, ILF, uncinate fasciculus, and internal and external capsules; interaction effects also extended across the genu, body, and splenium of the left hemisphere of the corpus callosum, and the left cingulum bundle.

Discussion

DTI-based studies examining WM diffusivity and anisotropy differences between healthy older adults and those with MCI are limited and have yielded variable results. Even fewer are the studies which have correlated neuropsychological measures with WM changes in MCI, with most of these having briefly detailed correlations with the MMSE (e.g., Bai et al., 2009; Chen et al., 2007; Duan et al., 2006), a measure not as sensitive to MCI as it is to AD (Bondi et al., 2008; Nasreddine et al., 2005; Tomabaugh et al., 1992). Here, RBANS indices were correlated with DTI-based diffusivity values to determine whether these indices are sensitive to WM degeneration in MCI, as this might aid in delineating the progression of neurodegeneration in AD.

Within group analyses yielded significant negative correlations ($p<0.05$) between DM and all three diffusivity indices, and between IM and DA, for the MCI group. DM correlations extended bilaterally along several fronto-parietal fiber pathways, including the SLF, FOF, and inferior longitudinal fasciculus (ILF; Table 2), and also included regions of the medial temporal lobes (MTLs). Correlations in these regions were in agreement with the hypotheses that DM scores would negatively correlate with diffusivity indices of the hippocampi and fronto-parietal fasciculi. Furthermore, DM scores were correlated with diffusivity changes in the corpus callosum and the internal capsule. It appears, then, that DM scores are sensitive to diffusivity changes in MCI along many pathways which have been shown to exhibit significantly different anisotropy or diffusivity scores between MCI and controls (Sexton et al., 2011). IM scores correlated with DA changes along the same pathways as for DM, but these correlations were restricted to the left hemisphere and did not include the MTLs.

RBANS DM and IM correlations

The current results indicated that RBANS DM scores demonstrated the most extensive correlations with WM diffusivity indices, supporting the traditional framework that MCI neurodegeneration has a primary impact upon episodic memory functioning. Furthermore, these extensive diffusivity correlations with DM are interesting because they suggest that memory impairment in MCI may result from or may be compounded by widespread WM degeneration. IM correlations with DA also argue for widespread WM neurodegeneration. IM correlations with DA overlapped with DM and DA correlations to a lesser extent than they did with DM correlations of DR and MD; the IM correlations included the left ILF and FOF which were not seen in DM correlations with DA. Because the RBANS DM index is based on the recall of information presented during IM assessment, implications of overall diffusivity changes in the relevant WM pathways are applicable to both.

The IM index score of the RBANS is derived from performance on list learning and story memory tests. During the list learning test subjects are asked to remember ten words while during the story memory test subjects are asked to remember a brief description of an event. The amount of information presented during either of these two tests exceeds the average immediate or short term memory capacity of four items (Cowan, 2001). Therefore, proper performance of these tests requires recruitment of the working memory system. Short-term memory performance is believed to be dependent on a fronto-parietal network associated with executive functioning and the focus of attention, while working memory performance is believed to have an added MTL

component which contributes to LTM process necessary for working memory performance (Champod & Petrides, 2007; Cowan 1999, Cowan 2005, Jonides & Nee, 2006, Unsworth & Engle, 2007; Vincent et al., 2008). Evidence from tracer and autoradiographic studies of non-human primates and diffusion imaging tractography of humans (Makris et al., 2005, 2007b; Petrides and Pandya, 1984, 2002, 2006; Schmahmann & Pandya, 2006; Schmahmann et al., 2007) indicates that frontal and parietal regions involved in working memory performance in the human brain, such as the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, inferior parietal lobule, superior parietal lobule, and the precuneus, appear to be connected by the SLF and FOF, both of which had diffusivity indices correlated with IM and DM scores.

Specifically, the SLF is thought to be a bi-directional pathway which has been shown to contain at least three subdivisions (SLF I, SLF II, and SLF III) in primates, and may contain a fourth subdivision, the arcuate fasciculus, in humans (Makris et al., 2005; Schmahmann & Pandya, 2006). SLF II is the major subdivision and connects the IPL and prefrontal cortex. SLF I and SLF III, meanwhile, connect the SPL and superior precuneus to the superior frontal gyrus, and the IPL to the VLPFC, respectively. Due to the inherent spatial limitations of the TBSS skeleton (values from surrounding voxels are averaged onto the skeleton) it is problematic to determine which portions of the SLF may be affected by neurodegenerative processes. Given the global nature of the correlations evidenced in the current study, however, it is not likely that neurodegenerative processes related to dementia target specific subdivisions of the SLF involved in memory functioning. Most DTI studies of MCI or AD which have reported anisotropy or diffusivity changes in the SLF have not identified specific subdivisions of the SLF.

Douaud et al. (2011), however, reported decreased FA and increased MD mostly in SLF II. Therefore, a possibility exists that SLF II exhibits greater initial vulnerability to neurodegeneration.

The FOF connects both lateral and medial parietal regions to the superior frontal gyrus and DLPFC and is thought to play roles in action tracking and reaching, and object discrimination and emotional reactivity (Makris et al., 2007a; Rizozolatti et al., 1990; Schmahmann and Pandya, 2007). Such functions do not appear to be necessary for working memory performance of verbally presented information during the RBANS IM test or recall during the DM test. The association of FOF diffusivity changes with performance on both tests is therefore not clear. One possibility for the correlation of FOF diffusivity indices with RBANS IM is that major fronto-parietal fasciculi like the FOF and SLF are equally vulnerable to the neurodegenerative effects of AD pathology (discussed in *Neurodegenerative mechanisms in mild cognitive impairment* sub-section). Alternatively, it may simply be that FOF plays a role in memory processes which are not currently known. Nevertheless, several DTI studies have reported anisotropy or diffusivity changes of the FOF in MCI and AD patients (Bosch et al., 2012).

The other major WM pathways exhibiting diffusivity correlations with IM and DM scores were the corpus callosum (splenium and body), inferior longitudinal fasciculus (ILF), and the internal capsule. In the non-human primate brain, the ILF has been identified as an association pathway that runs through the WM of the temporal, parietal, and occipital lobes, and also extends into the parahippocampal gyrus; it is the major pathway conducting information between the temporal and occipital cortices (Schmahmann & Pandya, 2006) and appears to subserve the ventral visual pathway, also

known as the “what” pathway. A recent DTI study by Wong et al. (2011) suggests ILF may form part of the ventral auditory/language stream, responsible for mapping speech or sounds to conceptual representations (Hickok & Poeppel, 2004, 2007). Wong et al. (2011) had participants learn associations between changes in pitch of a particular sound and an object, and then identified brain regions where FA predicted learning success of these associations. They found a significant cluster in a left parietal-temporal region and performed tractography from this region. Tractography results indicated that the ventral pathway was partly composed of a section of the ILF running along the middle temporal gyrus. Therefore, it is possible that in the current study IM and DM correlations with ILF may be linked to deficits in accessing conceptual, long term representations of sounds/words, which likely contributes to impaired memory functioning in MCI patients.

Anisotropy or diffusivity changes of the corpus callosum are commonly reported in DTI studies of MCI and AD (e.g., Bai et al., 2009, Chua et al., 2008, Duan et al., 2006; Liu et al., 2009, Zhang et al., 2007). Changes of the internal capsule have also been reported (Duan et al., 2006; Stahl et al., 2007; Stricker et al., 2009, but do not appear to be as common. The cognitive impact of corpus callosum and internal capsule neurodegeneration in MCI and AD is not clear. For example, the corpus callosum is the major commissural tract in the primate brain, but full or partial resections leave cognitive functioning remarkably intact (e.g., Mamelak et al., 1993). Very specific cognitive deficits, usually visuo-spatial or sensory, are only noted when patients undergo neuropsychological examination (e.g., Gazzaniga & Sperry, 1967). Palacios et al. (2011) did find that decreased FA of the corpus callosum correlated with working and declarative memory scores in those with traumatic brain injury. It is possible that in MCI

and AD altered anisotropy or diffusivity of the genu of the corpus callosum may contribute to impaired executive or memory function, since the genu is mainly responsible for inter-hemispheric frontal lobe communication.

RBANS DM scores and the hippocampal formation

The extensive correlations of RBANS DM scores with DA, DR, and MD in MCI suggest that global, bilateral WM deterioration plays a significant role in episodic memory impairment in MCI. The implications of neurodegeneration of major WM pathways which IM and DM scores both exhibited significant negative correlations with were just elaborated upon. These pathways were restricted to the left hemisphere, but DM scores also exhibited significant negative correlations with these pathways in the right hemisphere. More importantly, DM scores exhibited negative correlations with the left hippocampal formation.

There is abundant evidence which clearly links the hippocampal formation to memory formation, consolidation, and retrieval, and that damage to this region can significantly impair or prevent these processes (Insausti et al., 1987; Milner, 1972, Squire & Zola-Morgan, 1991; Zola-Morgan et al., 1994). Current knowledge of the neuroanatomical correlates of memory functioning and MCI/AD suggests that neurodegeneration of the hippocampal formation is the key cause of memory impairment in MCI/AD. Atrophy of the hippocampal formation is clearly evident on MRI scans and upon postmortem examination (Braak & Braak, 1991; Convit et al., 1993; Jack et al., 1992; Killiany et al., 2000); hippocampal formation atrophy is also sometimes evident on structural MRI scans of those with MCI (Atienza et al., 2011; Killiany et al., 2002; Wolf

et al., 2001). Thus, it is not surprising that the hypothesized negative correlations between DM and hippocampal diffusivity were evidenced. Furthermore, diffusivity and anisotropy changes of the hippocampus in MCI and AD have been frequently reported (Chen et al., 2007; Choo et al., 2010; Fellgiebel et al., 2004; Zhang et al., 2009).

Despite the fact the hippocampal formation is a complex structure consisting of multiple sub-regions including the three CA sub-fields, subiculum, dentate gyrus, and entorhinal cortex, and a couple of main fiber pathways, the fornix and the cingulum, many DTI studies, including the present one, are often limited to discussion of overall hippocampal changes. For instance, DTI studies often employ an in-plane resolution close to 2 x 2 mm, with a slice thickness often ranging from 2mm to 5mm. This results in partial voluming effects of the hippocampus which limit specificity, especially in regards to hippocampal WM pathways which are relatively small. A possible example of partial voluming effects may be seen in the Sexton et al. (2011) meta-analysis where a large effect size was reported for hippocampal FA and MD in MCI patients, but only a medium effect size was reported for hippocampal MD in AD patients. It is possible that studies which employed higher resolutions lacked the sensitivity to detect hippocampal changes, which resulted in a lower reported hippocampal effect size for AD than for MCI. The current study benefits from the use of TBSS, as one of the purposes of this method is to alleviate some of the problems associated with partial voluming effects. The TBSS skeleton, though, summarizes values surrounding the voxels of interest within the skeleton, which may still result in partial voluming of hippocampal WM. Consequently, DTI studies interested in hippocampal changes in AD and MCI will likely benefit by

acquiring high resolution diffusion weighted images of the hippocampal formation in order to reduce partial voluming effects and increase sub-region specificity.

Clear examples of the progression of specificity as higher resolutions and more advanced methods are used can be seen in volumetric imaging studies of the hippocampal formation. For example, Wolf et al. (2001) found that 75% of MCI patients were correctly classified based on hippocampal volume and also found that the left hippocampus exhibited greater volume reductions. Bozzali et al. (2006) reported reduced right parahippocampal / MTL gray matter volume in MCI converters, but not in non-converters, compared to controls. Additionally, they reported reduced right hippocampal gray matter volume in MCI converters compared to non-converters. Implementing more advanced techniques, Mueller et al. (2010) examined patterns of gray matter volume loss in hippocampal formation sub-regions. They reported that significant volume reductions in the CA1-CA2 transition area discriminated the best between MCI and controls, and that CA1 and CA1-CA2 transition area volume differences distinguished the best between AD and MCI. Interestingly, they reported that overall hippocampal volume was not a good discriminative measure for MCI or AD, but this may have been due to smaller sample sizes.

Neurodegenerative mechanisms in mild cognitive impairment

Typically, DTI studies analyzing changes in WM microstructure have used FA and MD as their metrics; the result of which has been significant cross study variability. Since FA and MD are derived from a tensor model, which is unable to correctly describe diffusion parameters in areas of crossing fibers (Mori & van Zijl, 2002; Wiegell et al.,

2000), they are prone to artificial alterations (Alexander et al., 2007Vos et al., 2012). Furthermore, when all three eigenvalues change proportionally in a voxel, FA may also lack sensitivity (Acosta-Cabronero et al., 2010). FA, therefore, appears to be the more problematic of these two common metrics, thus we opted to omit FA analyses. Based on the fact that in this study DA and DR correlations were noted in many of the same regions, it is possible that FA may have been insensitive to changes within these regions. As Acosta-Carbonero et al. (2010) noted, based on their lack of significant FA differences, changes in the size of the diffusion tensor are much more biologically plausible and informative than changes in anisotropy.

It is generally accepted that an increase in MD signifies a decrease in WM integrity. The interpretations of changes in DR, and especially DA, are not quite as clear. Changes in DR are thought to reflect changes in myelination, such that an increase in DR typically signifies compromised myelin integrity (Song et al., 2002, 2003, 2005). Decreased and increased DA values have both been attributed to pathological processes. Decreases in DA are thought to be indicative of intracellular breakdown (Glenn et al., 2003); while increases in DA are thought to be indicative of the removal of axonal fragments (Concha et al., 2006). A transition from an increase in DA to a decrease in DA therefore reflects the overall process of intracellular degeneration. For example, Mac Donald et al. (2007) caused traumatic brain injury in mice through a controlled cortical impact using an electromagnetic impact device. Mice were imaged at either 4-6 h, 24 h, 4 d, 1 week, or 1 month after injury. Results indicated that DA decreased acutely after injury and increased sub-acutely. Electron micrographs taken at subacute time points

revealed the presence of macrophages which had phagocytosed the damaged axons, many of which were still myelinated.

Explanations of the neuropathological process in MCI and AD based on diffusion abnormalities have revolved around hypotheses of Wallerian degeneration or retrogenesis. The Wallerian degeneration model of AD suggests a cascading effect of fiber pathway degeneration resulting from MTL compromise; changes in DA have often been interpreted as evidence for Wallerian degeneration (Huang & Auchus, 2007). The retrogenesis model suggests that late myelinating, small diameter fibers, such as neocortical association fibers and allocortical fibers, are most vulnerable to pathology and are the first to degenerate in AD (Bartzokis, 2004); changes in DR have therefore been interpreted as evidence of retrogenesis in AD. For example, Stricker et al. (2009) specifically aimed to test the retrogenesis model by examining anisotropy and diffusivity differences in early myelinating (posterior limb of internal capsule and cerebral peduncles) and late myelinating (SLF and ILF) pathways in AD and healthy older adults. They found no significant FA differences in early myelinating pathways, but found significant FA and DR differences in the ILF, indicating support for the retrogenesis model. However, differences in DA and DR were only examined where significant FA differences were first detected.

In the current study widespread and overlapping DM correlations with DA and DR were evidenced, with unique DR correlations along the left ILF and unique DA correlations along the left hippocampal formation. We do not believe that the latter unique correlations are sufficient to argue for either form of WM degeneration as other pathways which displayed diffusivity changes in both DA and DR did not show

significant differences between either change in diffusivity. Widespread interaction effects moderated by group categorization, however, were detected between DM scores and DR values. These interactions effects were evidenced along many of the same pathways already discussed, except for the hippocampal formation, but included the uncinate fasciculus, external capsule, and the cingulum bundle; most of these are late myelinating pathways. Due to the analysis methods employed in the current study, the direction of these interaction effects at any given voxel are not clear. These findings, though, are suggestive of changes in DR as the primary cause of WM degeneration and impaired memory functioning in MCI.

Limitations

There are a couple of limitations to this study which should be addressed. The first is that of MCI classification. Several methods have been proposed for classifying patients as MCI (e.g., Albert et al., 2011; Chang et al., 2011; Morris, 1993; O'Bryant et al., 2008; O'Bryant et al., 2010; Petersen et al., 1999) Here, we used a global CDR score of 0.5 as the criteria for classifying individuals as MCI. The use of a global CDR score of 0.5 has been previously supported (Morris, 1993), but it has been found that those with very mild dementia may be classified as MCI when solely using this criteria (Chang et al., 2011). An alternative staging guideline which has been shown to have good sensitivity and specificity is to assess the sum of boxes (SB) scores of the CDR (O'Bryant et al. 2008; 2010). Using this guideline, those with a GS of 0.5 and SB scores of 0.5-2.0 are classified as questionable dementia or MCI, while those with a GS of 0.5 and SB scores of 2.5-4.0 are classified as very mild dementia. The MCI sample for the

current study had a GS of 0.5 and an SB average of 1.16, demonstrating that the likelihood of having individuals with very mild dementia included in the MCI sample was very low.

An important decision in the analyses was to not control for level of education, even though the MCI group had significantly lower levels of education. It has been shown that individuals presenting with MCI or dementia often have lower levels of education than their age-matched controls (Anttila et al., 2002; Fratiglioni & Wang, 2007; Ngandu et al., 2007; Sattler et al., 2012; Stern et al., 1994). Level of education is often used as a proxy for cognitive reserve, or the ability of the brain to cope with injury by recruiting previously established and efficient processes, or implementing compensatory mechanisms (Stern, 2006). Therefore, level of education serves as a protective factor, such that those with higher levels of education who display similar levels of impairments as their age matched, but lesser educated peers, often exhibit more advanced stages of pathology and degeneration. Consequently, those individuals exhibit greater neuropathological deficits when compared to their healthy, age-matched controls and statistically controlling for level of education may artificially alter the variance in the functional findings attributable to cognitive impairment.

Conclusions

The value of using the RBANS in the assessment of AD has been well established, but its utility in assessing MCI is still under debate. Previous studies on the utility of the RBANS in MCI have noted that the memory subtests and retention scores from those subtests may have the greatest utility in the diagnosis of MCI (Clark et al.,

2010; Duff et al., 2010). Results from the current study indicated that RBANS DM scores correlated with widespread diffusivity changes across early myelinating (e.g., posterior limb of internal capsule), late myelinating (e.g., FOF, ILF, and SLF), and hippocampal WM in MCI. Strong correlations were found for IM scores, but were much more limited in scope. Additionally, DM scores demonstrated a between group interaction effect with DR in many of the pathways just discussed, along with the cingulum bundle, external capsule, and the uncinate fasciculus. It should be noted that in the current study, significant between group differences were not detected. The fact that RBANS DM scores were sensitive to diffusivity changes across a number of pathways suggests the DM index is a valuable tool in the assessment of WM damage. This is the first study that we are aware of to correlate WM microstructural changes with the RBANS in MCI, or in any impaired populations. Further studies investigating the relationship between RBANS indices and WM neurodegeneration in MCI and other impaired populations are warranted as they may provide clinically relevant information about patient prognosis.

References

Acosta-Cabronero, J., Williams, G.B., Pengas, G., Nestor, P.J., 2010. Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. Brain 133, 529-539.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 270-279.

Alexander, A.L., Lee, J.E., Lazar, M., Field, A.S., 2007. Diffusion tensor imaging of the brain. Neurotherapeutics 4, 316-329.

Anttila, T., Helkala, E.L., Kivipelto, M., Hallikainen, M., Alhainen, K., Heinonen, H., Mannermaa, A., Tuomilehto, J., Soininen, H., Nissinen, A., 2002. Midlife income, occupation, APOE status, and dementia: a population-based study. Neurology 59, 887-893.

Atienza, M., Atalaia-Silva, K.C., Gonzalez-Escamilla, G., Gil-Neciga, E., Suarez-Gonzalez, A., Cantero, J.L., 2011. Associative memory deficits in mild cognitive impairment: the role of hippocampal formation. Neuroimage 57, 1331-1342.

Bai, F., Zhang, Z., Watson, D.R., Yu, H., Shi, Y., Yuan, Y., Qian, Y., Jia, J., 2009. Abnormal integrity of association fiber tracts in amnestic mild cognitive impairment. J Neurol Sci 278, 102-106.

Bartzokis, G., 2004. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol Aging 25, 5-18; author reply 49-62.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed 15, 435-455.

Beaulieu, C., Allen, P.S., 1994. Determinants of anisotropic water diffusion in nerves. Magn Reson Med 31, 394-400.

Beaulieu, C., Does, M.D., Snyder, R.E., Allen, P.S., 1996. Changes in water diffusion due to Wallerian degeneration in peripheral nerve. Magn Reson Med 36, 627-631.

Behrens, T.E., Woolrich, M.W., Jenkinson, M., Johansen-Berg, H., Nunes, R.G., Clare, S., Matthews, P.M., Brady, J.M., Smith, S.M., 2003. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med 50, 1077-1088.

Blumenfeld, R.S., Ranganath, C., 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci 26, 916-925.

Blumenfeld, R.S., Ranganath, C., 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci 26, 916-925.

Bondi, M.W., Jak, A.J., Delano-Wood, L., Jacobson, M.W., Delis, D.C., Salmon, D.P., 2008. Neuropsychological contributions to the early identification of Alzheimer's disease. Neuropsychol Rev 18, 73-90.

Bosch, B., Arenaza-Urquijo, E.M., Rami, L., Sala-Llonch, R., Junque, C., Sole-Padulles, C., Pena-Gomez, C., Bargallo, N., Molinuevo, J.L., Bartres-Faz, D., 2012. Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. Neurobiol Aging 33, 61-74.

Bozzali, M., Falini, A., Franceschi, M., Cercignani, M., Zuffi, M., Scotti, G., Comi, G., Filippi, M., 2002. White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. J Neurol Neurosurg Psychiatry 72, 742-746.

Bozzali, M., Filippi, M., Magnani, G., Cercignani, M., Franceschi, M., Schiatti, E., Castiglioni, S., Mossini, R., Falautano, M., Scotti, G., Comi, G., Falini, A., 2006. The contribution of voxel-based morphometry in staging patients with mild cognitive impairment. Neurology 67, 453-460.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82, 239-259.

Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 2001. Prefrontal regions involved in keeping information in and out of mind. Brain 124, 2074-2086.

Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 2001. Prefrontal regions involved in keeping information in and out of mind. Brain 124, 2074-2086.

Champod, A.S., Petrides, M., 2007. Dissociable roles of the posterior parietal and the prefrontal cortex in manipulation and monitoring processes. Proc Natl Acad Sci USA 104, 14837-14842.

Chang, Y.L., Bondi, M.W., McEvoy, L.K., Fennema-Notestine, C., Salmon, D.P., Galasko, D., Hagler, D.J., Jr., Dale, A.M., Alzheimer's Disease Neuroimaging, I., 2011. Global clinical dementia rating of 0.5 in MCI masks variability related to level of function. Neurology 76, 652-659.

Chen, S.Q., Kang, Z., Hu, X.Q., Hu, B., Zou, Y., 2007. Diffusion tensor imaging of the brain in patients with Alzheimer's disease and cerebrovascular lesions. J Zhejiang Univ Sci B 8, 242-247.

Chen, S.Q., Kang, Z., Hu, X.Q., Hu, B., Zou, Y., 2007. Diffusion tensor imaging of the brain in patients with Alzheimer's disease and cerebrovascular lesions. J Zhejiang Univ Sci B 8, 242-247.

Choo, I.H., Lee, D.Y., Oh, J.S., Lee, J.S., Lee, D.S., Song, I.C., Youn, J.C., Kim, S.G., Kim, K.W., Jhoo, J.H., Woo, J.I., 2010. Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 31, 772-779.

Chua, T.C., Wen, W., Slavin, M.J., Sachdev, P.S., 2008. Diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease: a review. Curr Opin Neurol 21, 83-92.

Clark, J.H., Hobson, V.L., O'Bryant, S.E., 2010. Diagnostic accuracy of percent retention scores on RBANS verbal memory subtests for the diagnosis of Alzheimer's disease and mild cognitive impairment. Arch Clin Neuropsychol 25, 318-326.

Colliot, O., Chetelat, G., Chupin, M., Desgranges, B., Magnin, B., Benali, H., Dubois, B., Garnero, L., Eustache, F., Lehericy, S., 2008. Discrimination between Alzheimer disease, mild cognitive impairment, and normal aging by using automated segmentation of the hippocampus. Radiology 248, 194-201.

Concha, L., Gross, D.W., Wheatley, B.M., Beaulieu, C., 2006. Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. Neuroimage 32, 1090-1099.

Convit, A., de Leon, M.J., Golomb, J., George, A.E., Tarshish, C.Y., Bobinski, M., Tsui, W., De Santi, S., Wegiel, J., Wisniewski, H., 1993. Hippocampal atrophy in early Alzheimer's disease: anatomic specificity and validation. Psychiatr Q 64, 371-387.

Cowan, N., 1999. Mechanisms of active maintenance and executive control. In: Miyake, A., Shah, P. (Eds.), Models of Working Memory. Cambridge University Press, Cambridge, pp. 61-101.

Cowan, N., 2001. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. Behav Brain Sci 24, 87-114; discussion 114-185.

Cowan, N., 2005. Working memory capacity. Psychology Press, New York.

Cuetos, F., Arango-Lasprilla, J.C., Uribe, C., Valencia, C., Lopera, F., 2007. Linguistic changes in verbal expression: a preclinical marker of Alzheimer's disease. J Int Neuropsychol Soc 13, 433-439.

DeCarli, C., 2003. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2, 15-21.

D'Esposito, M., Postle, B.R., 1999. The dependence of span and delayed-response performance on prefrontal cortex. Neuropsychologia 37, 1303-1315.

Douaud, G., Jbabdi, S., Behrens, T.E., Menke, R.A., Gass, A., Monsch, A.U., Rao, A., Whitcher, B., Kindlmann, G., Matthews, P.M., Smith, S., 2011. DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. Neuroimage 55, 880-890.

Du, A.T., Schuff, N., Amend, D., Laakso, M.P., Hsu, Y.Y., Jagust, W.J., Yaffe, K., Kramer, J.H., Reed, B., Norman, D., Chui, H.C., Weiner, M.W., 2001. Magnetic

resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J Neurol Neurosurg Psychiatry 71, 441-447.

Duan, J.H., Wang, H.Q., Xu, J., Lin, X., Chen, S.Q., Kang, Z., Yao, Z.B., 2006. White matter damage of patients with Alzheimer's disease correlated with the decreased cognitive function. Surg Radiol Anat 28, 150-156.

Duff, K., Hobson, V.L., Beglinger, L.J., O'Bryant, S.E., 2010. Diagnostic accuracy of the RBANS in mild cognitive impairment: limitations on assessing milder impairments. Arch Clin Neuropsychol 25, 429-441.

Fama, R., Sullivan, E.V., Shear, P.K., Cahn-Weiner, D.A., Marsh, L., Lim, K.O., Yesavage, J.A., Tinklenberg, J.R., Pfefferbaum, A., 2000. Structural brain correlates of verbal and nonverbal fluency measures in Alzheimer's disease. Neuropsychology 14, 29-40.

Fellgiebel, A., Wille, P., Muller, M.J., Winterer, G., Scheurich, A., Vucurevic, G., Schmidt, L.G., Stoeter, P., 2004. Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. Dement Geriatr Cogn Disord 18, 101-108.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. J Neurosci 29, 15223-15231.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12, 189-198.

Fratiglioni, L., Wang, H.X., 2007. Brain reserve hypothesis in dementia. J Alzheimers Dis 12, 11-22.

Gazzaniga, M.S., Sperry, R.W., 1967. Language after section of the cerebral commissures. Brain 90, 131-148.

Glenn, O.A., Henry, R.G., Berman, J.I., Chang, P.C., Miller, S.P., Vigneron, D.B., Barkovich, A.J., 2003. DTI-based three-dimensional tractography detects differences in the pyramidal tracts of infants and children with congenital hemiparesis. J Magn Reson Imaging 18, 641-648.

Gold, G., Giannakopoulos, P., Herrmann, F.R., Bouras, C., Kovari, E., 2007. Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain 130, 2830-2836.

Grober, E., Hall, C.B., Lipton, R.B., Zonderman, A.B., Resnick, S.M., Kawas, C., 2008. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Int Neuropsychol Soc 14, 266-278.

Heo, J.H., Lee, S.T., Kon, C., Park, H.J., Shim, J.Y., Kim, M., 2009. White matter hyperintensities and cognitive dysfunction in Alzheimer disease. J Geriatr Psychiatry Neurol 22, 207-212.

Hickok, G., 2009. The functional neuroanatomy of language. Phys Life Rev 6, 121-143.

Hickok, G., Poeppel, D., 2004. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition 92, 67-99.

Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nat Rev Neurosci 8, 393-402.

Huang, J., Auchus, A.P., 2007. Diffusion tensor imaging of normal appearing white matter and its correlation with cognitive functioning in mild cognitive impairment and Alzheimer's disease. Ann N Y Acad Sci 1097, 259-264.

Hughes, C.P., Berg, L., Danziger, W.L., Coben, L.A., Martin, R.L., 1982. A new clinical scale for the staging of dementia. Br J Psychiatry 140, 566-572.

Insausti, R., Amaral, D.G., Cowan, W.M., 1987. The entorhinal cortex of the monkey: II. Cortical afferents. J Comp Neurol 264, 356-395.

Jack, C.R., Jr., Petersen, R.C., O'Brien, P.C., Tangalos, E.G., 1992. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 42, 183-188.

Jenkinson, M., 2003. A fast, automated, N-dimensional phase-unwrapping algorithm. Magn Reson Med 49, 193-197.

Jonides, J., Nee, D.E., 2006. Brain mechanisms of proactive interference in working memory. Neuroscience 139, 181-193.

Kavcic, V., Ni, H., Zhu, T., Zhong, J., Duffy, C.J., 2008. White matter integrity linked to functional impairments in aging and early Alzheimer's disease. Alzheimers Dement 4, 381-389.

Killiany, R.J., Gomez-Isla, T., Moss, M., Kikinis, R., Sandor, T., Jolesz, F., Tanzi, R., Jones, K., Hyman, B.T., Albert, M.S., 2000. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 47, 430-439.

Killiany, R.J., Hyman, B.T., Gomez-Isla, T., Moss, M.B., Kikinis, R., Jolesz, F., Tanzi, R., Jones, K., Albert, M.S., 2002. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 58, 1188-1196.

Levelt, W.J., Praamstra, P., Meyer, A.S., Helenius, P., Salmelin, R., 1998. An MEG study of picture naming. J Cogn Neurosci 10, 553-567.

Liu, Y., Spulber, G., Lehtimaki, K.K., Kononen, M., Hallikainen, I., Grohn, H., Kivipelto, M., Hallikainen, M., Vanninen, R., Soininen, H., 2011. Diffusion tensor imaging and tract-based spatial statistics in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 32, 1558-1571.

Liu, Y., Spulber, G., Lehtimaki, K.K., Kononen, M., Hallikainen, I., Grohn, H., Kivipelto, M., Hallikainen, M., Vanninen, R., Soininen, H., 2011. Diffusion tensor imaging and tract-based spatial statistics in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 32, 1558-1571.

Mac Donald, C.L., Dikranian, K., Bayly, P., Holtzman, D., Brody, D., 2007. Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. J Neurosci 27, 11869-11876.

Makris, N., Kennedy, D.N., McInerney, S., Sorensen, A.G., Wang, R., Caviness, V.S., Jr., Pandya, D.N., 2005. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb Cortex 15, 854-869.

Makris, N., Papadimitriou, G.M., Sorg, S., Kennedy, D.N., Caviness, V.S., Pandya, D.N., 2007. The occipitofrontal fascicle in humans: a quantitative, in vivo, DT-MRI study. Neuroimage 37, 1100-1111.

Makris, N., Papadimitriou, G.M., van der Kouwe, A., Kennedy, D.N., Hodge, S.M., Dale, A.M., Benner, T., Wald, L.L., Wu, O., Tuch, D.S., Caviness, V.S., Moore, T.L., Killiany, R.J., Moss, M.B., Rosene, D.L., 2007. Frontal connections and cognitive

changes in normal aging rhesus monkeys: a DTI study. Neurobiol Aging 28, 1556-1567.

Mamelak, A.N., Barbaro, N.M., Walker, J.A., Laxer, K.D., 1993. Corpus callosotomy: a quantitative study of the extent of resection, seizure control, and neuropsychological outcome. J Neurosurg 79, 688-695.

Medina, D., DeToledo-Morrell, L., Urresta, F., Gabrieli, J.D., Moseley, M., Fleischman, D., Bennett, D.A., Leurgans, S., Turner, D.A., Stebbins, G.T., 2006. White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. Neurobiol Aging 27, 663-672.

Melhem, E.R., Mori, S., Mukundan, G., Kraut, M.A., Pomper, M.G., van Zijl, P.C., 2002. Diffusion tensor MR imaging of the brain and white matter tractography. AJR Am J Roentgenol 178, 3-16.

Milner, B., 1972. Disorders of learning and memory after temporal lobe lesions in man. Clin Neurosurg 19, 421-446.

Mori, S., van Zijl, P.C., 2002. Fiber tracking: principles and strategies - a technical review. NMR Biomed 15, 468-480.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412-2414.

Morris, J.C., 1997. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 9 Suppl 1, 173-176; discussion 177-178.

Mueller, S.G., Schuff, N., Yaffe, K., Madison, C., Miller, B., Weiner, M.W., 2010. Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 31, 1339-1347.

Muller, M.J., Greverus, D., Weibrich, C., Dellani, P.R., Scheurich, A., Stoeter, P., Fellgiebel, A., 2007. Diagnostic utility of hippocampal size and mean diffusivity in amnestic MCI. Neurobiol Aging 28, 398-403.

Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53, 695-699.

Ngandu, T., von Strauss, E., Helkala, E.L., Winblad, B., Nissinen, A., Tuomilehto, J., Soininen, H., Kivipelto, M., 2007. Education and dementia: what lies behind the association? Neurology 69, 1442-1450.

Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15, 1-25.

O'Bryant, S.E., Lacritz, L.H., Hall, J., Waring, S.C., Chan, W., Khodr, Z.G., Massman, P.J., Hobson, V., Cullum, C.M., 2010. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 67, 746-749.

O'Bryant, S.E., Waring, S.C., Cullum, C.M., Hall, J., Lacritz, L., Massman, P.J., Lupo, P.J., Reisch, J.S., Doody, R., 2008. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol 65, 1091-1095.

Palacios, E.M., Fernandez-Espejo, D., Junque, C., Sanchez-Carrion, R., Roig, T., Tormos, J.M., Bargallo, N., Vendrell, P., 2011. Diffusion tensor imaging differences relate to memory deficits in diffuse traumatic brain injury. BMC Neurol 11, 24.

Panza, F., D'Introno, A., Colacicco, A.M., Capurso, C., Del Parigi, A., Caselli, R.J., Pilotto, A., Argentieri, G., Scapicchio, P.L., Scafato, E., Capurso, A., Solfrizzi, V., 2005. Current epidemiology of mild cognitive impairment and other predementia syndromes. Am J Geriatr Psychiatry 13, 633-644.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J Intern Med 256, 183-194.

Petersen, R.C., Bennett, D., 2005. Mild cognitive impairment: is it Alzheimer's disease or not? J Alzheimers Dis 7, 241-245; discussion 255-262.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., Winblad, B., 2001. Current concepts in mild cognitive impairment. Arch Neurol 58, 1985-1992.

Petrides, M., Pandya, D.N., 1984. Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. J Comp Neurol 228, 105-116.

Petrides, M., Pandya, D.N., 2002. Association pathways of the prefrontal cortex and functional observations. In: Stuss, D.T., Knight, R.T. (Eds.), Principles of frontal lobe function. Oxford University Press, New York, pp. 31-50.

Petrides, M., Pandya, D.N., 2006. Efferent association pathways originating in the caudal prefrontal cortex in the macaque monkey. J Comp Neurol 498, 227-251.

Pierpaoli, C., Jezzard, P., Basser, P.J., Barnett, A., Di Chiro, G., 1996. Diffusion tensor MR imaging of the human brain. Radiology 201, 637-648.

Pierpaoli, C., Jezzard, P., Basser, P.J., Barnett, A., Di Chiro, G., 1996. Diffusion tensor MR imaging of the human brain. Radiology 201, 637-648.

Postle, B.R., Druzgal, T.J., D'Esposito, M., 2003. Seeking the neural substrates of visual working memory storage. Cortex 39, 927-946.

Randolph, C., 1998. Repeatable battery for the assessment of neuropsychological status. The Psychological Corporation, San Antonio, Tx.

Rapp, M.A., Reischies, F.M., 2005. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). Am J Geriatr Psychiatry 13, 134-141.

Rizzolatti, G., Gentilucci, M., Camarda, R.M., Gallese, V., Luppino, G., Matelli, M., Fogassi, L., 1990. Neurons related to reaching-grasping arm movements in the rostral part of area 6 (area 6a beta). Exp Brain Res 82, 337-350.

Roach, E.S., 2005. Treating mild cognitive impairment: The absence of evidence. Arch Neurol 62, 1167.

Rose, S.E., Janke, A.L., Chalk, J.B., 2008. Gray and white matter changes in Alzheimer's disease: a diffusion tensor imaging study. J Magn Reson Imaging 27, 20-26.

Salat, D.H., Greve, D.N., Pacheco, J.L., Quinn, B.T., Helmer, K.G., Buckner, R.L., Fischl, B., 2009. Regional white matter volume differences in nondemented aging and Alzheimer's disease. Neuroimage 44, 1247-1258.

Salat, D.H., Tuch, D.S., van der Kouwe, A.J., Greve, D.N., Pappu, V., Lee, S.Y., Hevelone, N.D., Zaleta, A.K., Growdon, J.H., Corkin, S., Fischl, B., Rosas, H.D.,

2010. White matter pathology isolates the hippocampal formation in Alzheimer's disease. Neurobiol Aging 31, 244-256.

Sattler, C., Toro, P., Schonknecht, P., Schroder, J., 2012. Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. Psychiatry Res 196, 90-95.

Schmahmann, J.D., Pandya, D.N., 2006. Fiber pathways in the brain. Oxford University Press, New York.

Schmahmann, J.D., Pandya, D.N., 2007. The complex history of the fronto-occipital fasciculus. J Hist Neurosci 16, 362-377.

Sexton, C.E., Kalu, U.G., Filippini, N., Mackay, C.E., Ebmeier, K.P., 2011. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 32, 2322 e2325-2318.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487-1505.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 Suppl 1, S208-219.

Song, S.K., Sun, S.W., Ju, W.K., Lin, S.J., Cross, A.H., Neufeld, A.H., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 20, 1714-1722.

Song, S.K., Sun, S.W., Ramsbottom, M.J., Chang, C., Russell, J., Cross, A.H., 2002. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 17, 1429-1436.

Song, S.K., Yoshino, J., Le, T.Q., Lin, S.J., Sun, S.W., Cross, A.H., Armstrong, R.C., 2005. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage 26, 132-140.

Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu Rev Neurosci 27, 279-306.

Squire, L.R., Zola-Morgan, S., 1991. The medial temporal lobe memory system. Science 253, 1380-1386.

Stahl, R., Dietrich, O., Teipel, S.J., Hampel, H., Reiser, M.F., Schoenberg, S.O., 2007. White matter damage in Alzheimer disease and mild cognitive impairment: assessment with diffusion-tensor MR imaging and parallel imaging techniques. Radiology 243, 483-492.

Stern, Y., 2006. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord 20, 112-117.

Stern, Y., Gurland, B., Tatemichi, T.K., Tang, M.X., Wilder, D., Mayeux, R., 1994. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 271, 1004-1010.

Stricker, N.H., Schweinsburg, B.C., Delano-Wood, L., Wierenga, C.E., Bangen, K.J., Haaland, K.Y., Frank, L.R., Salmon, D.P., Bondi, M.W., 2009. Decreased white matter integrity in late-myelinating fiber pathways in Alzheimer's disease supports retrogenesis. Neuroimage 45, 10-16.

Tombaugh, T.N., McIntyre, N.J., 1992. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 40, 922-935.

Twamley, E.W., Ropacki, S.A., Bondi, M.W., 2006. Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. J Int Neuropsychol Soc 12, 707-735.

Unsworth, N., Engle, R.W., 2007. The nature of individual differences in working memory capacity: active maintenance in primary memory and controlled search from secondary memory. Psychol Rev 114, 104-132.

Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L., 2008. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol 100, 3328-3342.

Vos, S.B., Jones, D.K., Jeurissen, B., Viergever, M.A., Leemans, A., 2012. The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain. Neuroimage 59, 2208-2216.

Wiegell, M.R., Larsson, H.B., Wedeen, V.J., 2000. Fiber crossing in human brain depicted with diffusion tensor MR imaging. Radiology 217, 897-903.

Wilcke, J.C., O'Shea, R.P., Watts, R., 2009. Frontoparietal activity and its structural connectivity in binocular rivalry. Brain Res 1305, 96-107.

Wind, A.W., Schellevis, F.G., Van Staveren, G., Scholten, R.P., Jonker, C., Van Eijk, J.T., 1997. Limitations of the Mini-Mental State Examination in diagnosing dementia in general practice. Int J Geriatr Psychiatry 12, 101-108.

Wolf, H., Grunwald, M., Kruggel, F., Riedel-Heller, S.G., Angerhofer, S., Hojjatoleslami, A., Hensel, A., Arendt, T., Gertz, H., 2001. Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly. Neurobiol Aging 22, 177-186.

Wong, F.C., Chandrasekaran, B., Garibaldi, K., Wong, P.C., 2011. White matter anisotropy in the ventral language pathway predicts sound-to-word learning success. J Neurosci 31, 8780-8785.

Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. Neuroimage 45, S173-186.

Yasmin, H., Nakata, Y., Aoki, S., Abe, O., Sato, N., Nemoto, K., Arima, K., Furuta, N., Uno, M., Hirai, S., Masutani, Y., Ohtomo, K., 2008. Diffusion abnormalities of the uncinate fasciculus in Alzheimer's disease: diffusion tensor tract-specific analysis using a new method to measure the core of the tract. Neuroradiology 50, 293-299.

Zhang, Y., Schuff, N., Du, A.T., Rosen, H.J., Kramer, J.H., Gorno-Tempini, M.L., Miller, B.L., Weiner, M.W., 2009. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. Brain 132, 2579-2592.

Zhang, Y., Schuff, N., Jahng, G.H., Bayne, W., Mori, S., Schad, L., Mueller, S., Du, A.T., Kramer, J.H., Yaffe, K., Chui, H., Jagust, W.J., Miller, B.L., Weiner, M.W.,

2007. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. Neurology 68, 13-19.

Zola-Morgan, S., Squire, L.R., Ramus, S.J., 1994. Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. Hippocampus 4, 483-495.

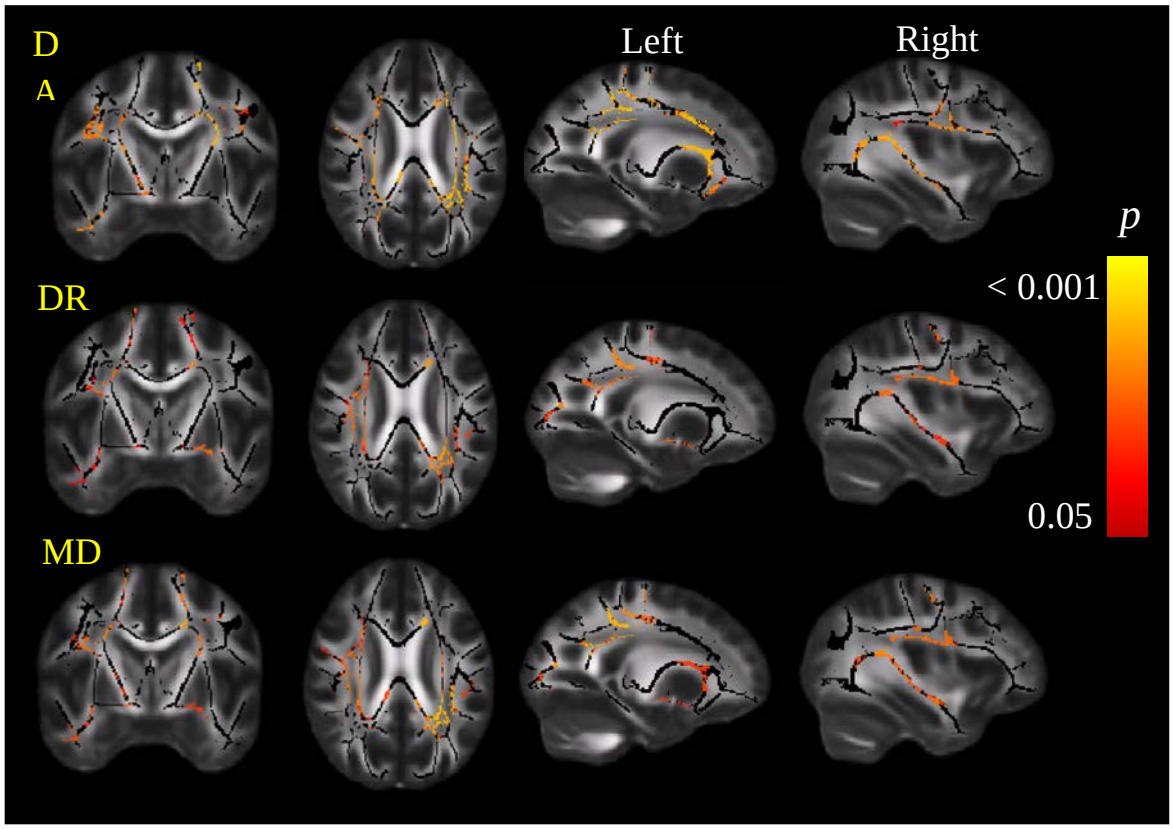

Figure 4.1. Significant RBANS DM correlations. Significant TBSS correlations for the MCI group with respect to RBANS DM scores. *Top*. Correlations between DM scores and DA. *Middle*. Correlations between DM scores and DR. *Bottom.* Correlations between DM scores and MD. Images are in radiologic orientation.

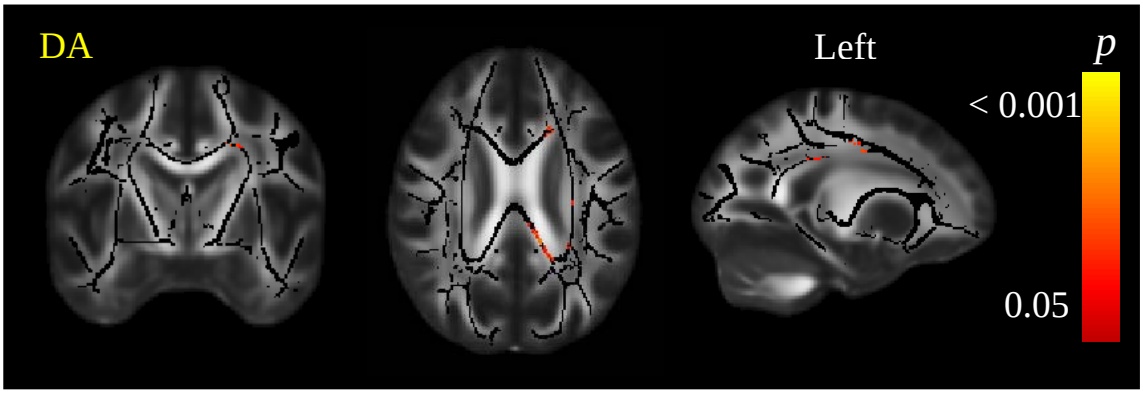

Figure 4.2. Significant RBANS IM correlations. Significant TBSS correlations for the MCI group with respect to RBANS IM scores.

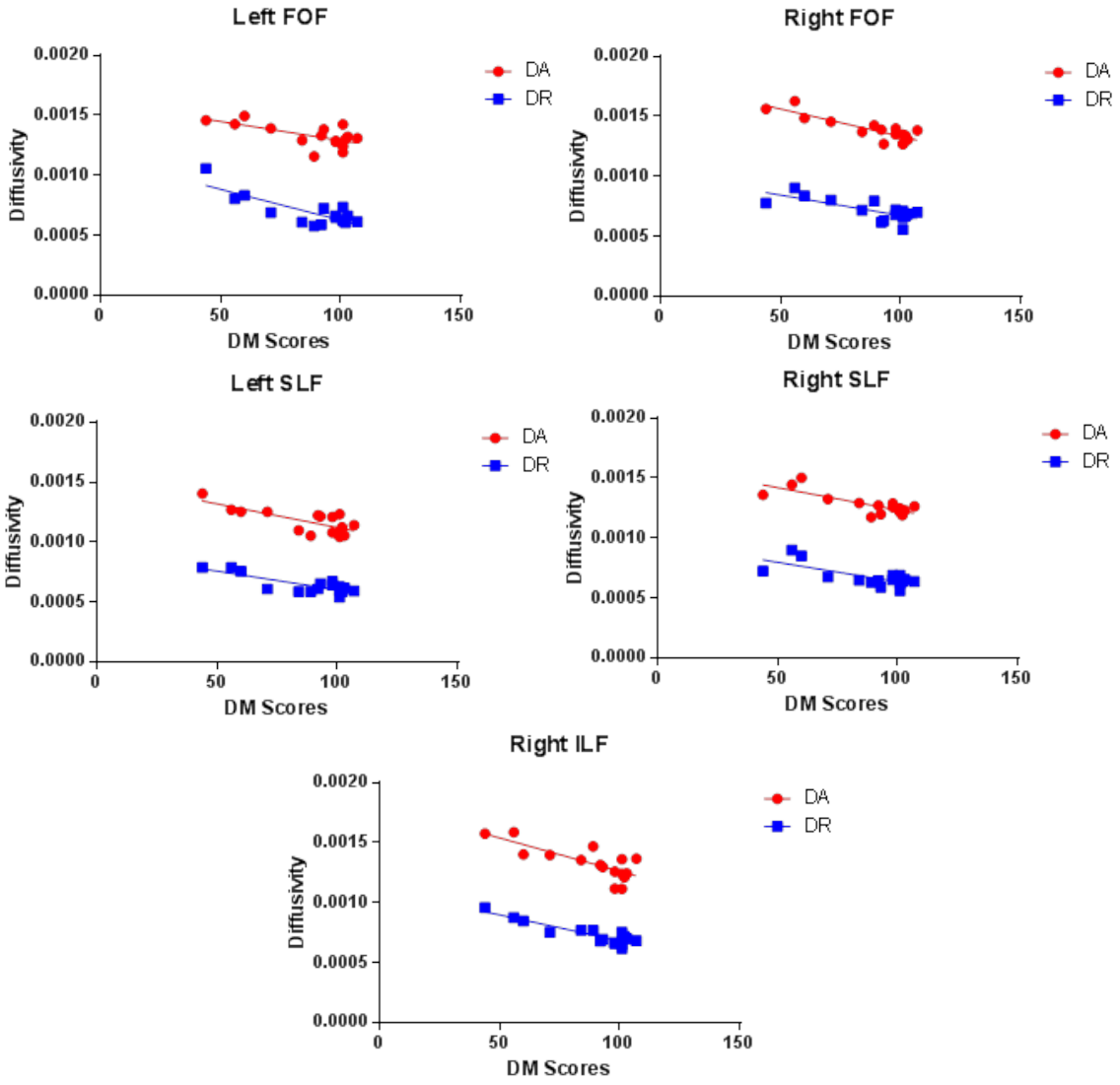

Figure 4.3. DA and DR comparisons. Graphs depicting the slope of DA and DR values of fiber tracts which evidenced significant correlations in MCI for both of these diffusivity measures and for which a well-defined mask was available to extract the appropriate values. Pairs of DA and DR values did not exhibit significantly different slopes, indicating white matter degeneration may not have been proceeding along a preferred axis.

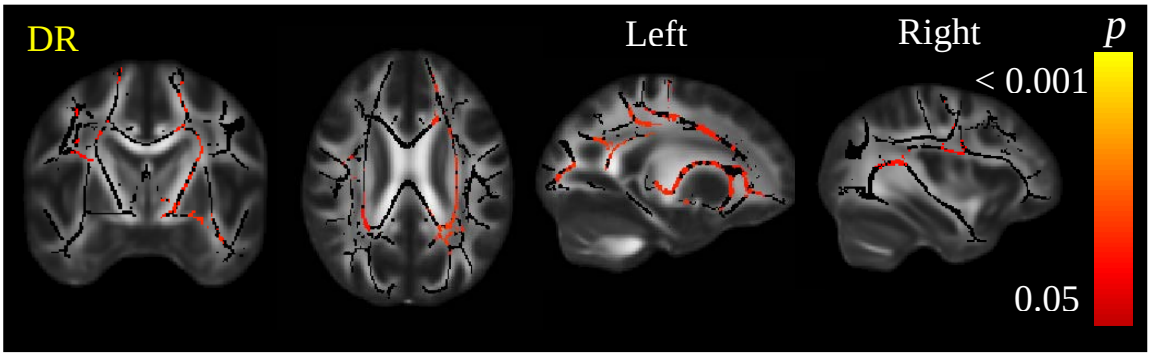

Figure 4.4. Significant RBASN DM and DR interaction effects. Signifincat TBSS interactions effects between DM and DR moderated by group.

Table 4.1
Demographic and cognitive scores.

	Control Group Avg.	MCI Group Avg.	*t*-Test	p value
Age	74.17 (5.50)	75.13 (6.53)	0.50	0.6193
Education	16.96 (2.33)	14.19 (3.47)	3.03	0.0044*
Immediate Memory	103.9 (18.01)	86.13 (15.62)	3.22	0.0013*
Visuospatial	102.0 (10.63)	95.94 (17.15)	1.34	0.0935
Language	103.1 (10.18)	90.19 (18.24)	2.87	0.0034*
Attention	108.1 (16.94)	93.75 (12.91)	2.87	0.0033*
Delayed Memory	103.6 (13.93)	87.50 (19.28)	3.07	0.0020*

* Indicates significant differences between groups.

Table 4.2
White matter pathways demonstrating significant correlations.

White matter pathways	Delayed Memory			Immediate Memory	Delayed Memory Interaction
Diffusivity Index	DA	DR	MD	DA	DR
Superior longitudinal fasciculus	B	B	B	L	B
Fronto-occipital fasciculus	B	B	B	L	B
Inferior longitudinal fasciculus	R	B	B	L	B
Hippocampal	L	B	L	L	-
Internal capsule, posterior / corticospinal	L	R	R	L	B
Corpus callosum	L	B	L	L	L
Uncinate fasciculus	-	-	-	-	B
External capsule	-	-	-	-	B
Cingulum bundle	-	-	-	-	L

Delayed and Immediate memory scores are in respect to the MCI group. The delayed memory interaction is in respect to group categorization.
B = Bilateral. L = Left hemisphere. R = Right hemisphere.

CHAPTER 5

CONCLUSION

This study aimed to discover novel biomarkers of mild cognitive impairment (MCI) using two different magnetic resonance imaging (MRI) modalities, functional MRI (fMRI) and diffusion tensor imaging (DTI). Specifically, fMRI data were acquired while participants performed a complex working memory span (CWKMS) task, and DTI diffusivity values were correlated with cognitive indices from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). This is the first study, to the author's knowledge, to acquire fMRI data on MCI patients while they performed a CWMS task and to correlate RBANS indices with DTI diffusivity values in MCI, or any other populations.

In comparing functional activity during the CWKMS for the MCI group to the healthy older adult control group, it was found that during encoding and maintenance MCI patients exhibited increased activation in the superior temporal gyrus (STG) and the medial temporal gyrus (MTL), particularly in the parahippocampal gyrus and the hippocampus. Functional differences in the MTL were expected based on previous research, but such localized differences in regions of the STG responsible for speech perception and production, necessary for the maintenance of information, were quite novel. Previous work on MCI, but especially Alzheimer's disease (AD), has suggested that the memory impairments experienced by these populations are a result of poor memory encoding (Germano & Kinsella, 2005; White & Ruske, 2002). If taken within this framework, the current fMRI findings suggest that MCI patients increase their level

of rehearsal in order to properly encode relevant information; the rehearsal of information is known to strengthen memory encoding. Alternatively, the current findings may also suggest that MCI patients experience deficits in information rehearsal or the maintenance of information in the focus of attention as a result of STG neuropathology. Functional impairment of the STG would be consistent with theories that AD-related neurodegeneration propagates outwards from the MTLs (Alafuzoff et al., 2008; Braak & Braak, 1991).

DTI diffusivity correlations with RBANS indices indicated that the delayed memory (DM) index correlated with widespread axial (DA), radial (DR), and mean diffusivity (MD) changes in those with MCI, but not in controls. These changes occurred along three of the major anterior-posterior associative fiber pathways of the brain, the superior longitudinal fasciculus, fronto-occipital fasciculus, and the inferior longitudinal fasciculus, along with the internal capsule, corpus callosum, and the hippocampal white matter. Immediate memory scores (IM) from the RBANS also correlated with DA changes across the left hemisphere of many of these regions. Significant, widespread interaction effects between the groups for DM scores in relation to DR may be indicative of the ongoing neurodegenerative process in MCI and AD, as increased DR is thought to be indicative of retrogenesis. This finding supports previous work indicating that retrogenesis may be the main neurodegenerative process occurring in AD, but must be taken with caution as this result was found in relation to a neuropsychological exam and not a straightforward comparison of diffusivity changes between groups.

These correlations indicate that portions of the RBANS are sensitive to WM neurodegeneration in those with MCI and may have some further clinical utility. It is

possible, though, that other measures derived from the RBANS may have overall greater clinical utility than DM and IM scores due to the widespread changes DM and IM correlated with. For example, the memory related subtests of the RBANS have been shown to have high specificity but low sensitivity (Duff et al., 2010), while percent retention scores from the List Learning and Story Memory subtests have displayed excellent specificity and sensitivity (Clark et al., 2010).

Overall, this study yielded novel insights into the functional and structural changes that accompany impaired memory functioning in MCI. DTI diffusivity correlations suggest the impaired long term memory functioning in MCI may be compounded by global white matter degeneration, rather than just MTL degeneration; while functional imaging results suggest that STG dysfunction contributes to working memory related changes in MCI. As this is the first study to employ fMRI with CWKMS tasks in MCI and to correlate RBANS scores with diffusivity in MCI, future studies should aim to not only replicate these findings but to improve upon the methods used. For example, other CWKMS tasks or more taxing versions of the current CWKMS task could be employed to elicit broad behavioral differences between MCI and control groups, as this may further reveal novel findings. Additionally, other cognitive measures may be correlated with diffusivity changes as there are numerous neuropsychological tools available which may possess higher specificity and sensitivity to MCI than the RBANS.

References

Alafuzoff, I., Arzberger, T., Al-Sarraj, S., Bodi, I., Bogdanovic, N., Braak, H., Bugiani, O., Del-Tredici, K., Ferrer, I., Gelpi, E., Giaccone, G., Graeber, M.B., Ince, P., Kamphorst, W., King, A., Korkolopoulou, P., Kovacs, G.G., Larionov, S., Meyronet, D., Monoranu, C., Parchi, P., Patsouris, E., Roggendorf, W., Seilhean, D., Tagliavini, F., Stadelmann, C., Streichenberger, N., Thal, D.R., Wharton, S.B., Kretzschmar, H., 2008. Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium. Brain Pathol 18, 484-496.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82, 239-259.

Clark, J.H., Hobson, V.L., O'Bryant, S.E., 2010. Diagnostic accuracy of percent retention scores on RBANS verbal memory subtests for the diagnosis of Alzheimer's disease and mild cognitive impairment. Arch Clin Neuropsychol 25, 318-326.

Duff, K., Hobson, V.L., Beglinger, L.J., O'Bryant, S.E., 2010. Diagnostic accuracy of the RBANS in mild cognitive impairment: limitations on assessing milder impairments. Arch Clin Neuropsychol 25, 429-441.

Germano, C., Kinsella, G.J., 2005. Working memory and learning in early Alzheimer's disease. Neuropsychol Rev 15, 1-10.

White, K.G., Ruske, A.C., 2002. Memory deficits in Alzheimer's disease: the encoding hypothesis and cholinergic function. Psychon Bull Rev 9, 426-437.